YOUTH AND ADOLESCENTS WITH TYPE 1 DIABETES IN THE LIFE FOR A CHILD PROGRAM IN RWANDA, AFRICA

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ABSTRACT

An estimated 285 million people had diabetes in 2010 of whom 480,000 were <14 years of age and most likely had type 1 diabetes (T1D). Each year, an additional 76,000 cases are diagnosed and incidence is increasing. Because there is no cure for T1D, this is an issue of great public health concern, particularly in developing countries, which will need to continue providing care for communicable diseases while addressing the rising incidence of chronic diseases.

To fully address the growing issue of T1D in developing countries, we need to better understand the true burden of the disease (incidence/prevalence), how it presents and progresses, and how to prevent early mortality. This dissertation represents the first attempt to describe these measures, in Rwandan youth and adolescents, with T1D and is based on collaboration with the Life For a Child program and the Association Rwandaise des Diabetiques.

Our data suggest that the rates of T1D in Rwanda are relatively low compared to African-Arabic countries, but similar to neighboring Tanzania. Incidence of recognized T1D has, however, increased over the last ten years, portending a larger issue in the near future. Additional efforts are needed to ensure proper and timely diagnosis, as it appears likely that cases are dying before diagnosis, or are being misdiagnosed, especially in those <5 years of age.

While the mortality rate in Rwanda was similar to several other African countries, it was significantly higher than rates seen in developed countries, and hypoglycemia was a major cause of death. We did, however, demonstrate that glycemic control could be improved in a country with limited resources, and confirmed that more frequent glucose monitoring is a potential intervention strategy.

Though these results are promising, it is clear that further research and interventions are needed to adequately address T1D in Rwanda. Additional efforts are needed to address the issue of balancing glycemic control and fear of hypoglycemia, especially in this population where food insecurity is common. Finally, additional strides need to be taken towards making this program more sustainable long-term, so that proper care may be available well into the future.

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PREFACE

When I arrived in Pittsburgh in the fall of 2008, I never imagined so much would change after attending Dr. Orchard's Epidemiology seminar. That one decision to approach him and express my interest forever changed me as a student and as a person. The subsequent trips to Rwanda provided me with the chance to experience a culture significantly different than ours, introduced me to some of the most amazingly wonderful people, and allowed me to actually impact the lives of others through my research.

I would like to thank Dr. Orchard and my committee members for the continued guidance and mentorship, and Drs. Deborah Edidin and Graham Ogle for the constant support and encouragement. I would also like to thank my family for understanding my desire to travel to this far off land and for putting up with the inflated phone bills, the obnoxious number of photos upon my return, and the minor panic attacks while compiling this dissertation. I would also like to thank my fiancé, Michael, for being patient and my #1 cheerleader throughout this process, as I "ran away" for weeks at a time to a place with a slow internet connection. His Skype conversations, cards, snacks, and gifts went a long way towards making my trips and the writing process as comfortable and painless as possible. I have a wonderful co-worker in Laurien Sibomana, and his help and friendship throughout this process should be commended, as should the efforts of the MPH students who aided me in data collection over the last several years.

Finally, the majority of my praise and thanks goes to the wonderful ARD staff (Francois Gishoma, Vedaste Kaberuka, Crispin Gishoma, et al) and the children they care for. This project would not have been possible without their willingness to open up their program and hearts to us, and I know that I will have life-long friends and colleagues.

1.0 INTRODUCTION

Abdel Omran first described the phenomenon of the epidemiologic transition of disease in 1971 as a process where "degenerative and man-made diseases displace pandemics of infection as the primary causes of morbidity and mortality." This shift occurs as countries become more developed and design more comprehensive public health infrastructures which result in lower mortality due to communicable diseases and increases in average life expectancy.[1] As people live longer, they have more time to develop chronic or non-communicable diseases (NCDs). This shift has already occurred in the United States, and can now be seen in developing countries. Globally, an estimated 8-14 million people die yearly due to such preventable NCDs; 80% of whom lived in developing countries.[2] Currently, communicable diseases are the focus of most public health efforts in developing countries, but as more countries go through this transition, it will become increasingly necessary for officials to focus not just on communicable diseases, but on NCDs as well.

This thesis will focus on one such NCD of increasing importance in the Developing World – diabetes. The rates of this disease have risen over the last several years and are expected to increase substantially into the future. While this disease was once thought of as a disease of the wealthy, it is quickly becoming a disease associated with low- and middle- incomes, with a disproportionate burden being carried by individuals of low socio-economic status. An estimated 380 million people world-wide will be affected by this disease by 2025, with 18.7 million residing in sub-Saharan Africa.[2]

2.0 BACKGROUND

2.1 DEFINITION OF DIABETES MELLITUS

To appreciate the individual burden of this disease in developing countries, it is necessary to first understand the basic pathophysiology of this disease. The term “diabetes” refers to an assemblage of diseases where there is a disruption of either the body’s ability to produce or respond to insulin (or both) resulting in increased levels of blood glucose (figure 1). Insulin is a peptide hormone that is released by β- cells located in the Islets of Langerhans of the pancreas. Insulin is used by liver, muscle and adipose cells to take up glucose from the bloodstream for energy production. When insulin is not present in sufficient levels or is unable to be used by the cells properly, those cells are unable to function properly and glucose builds up in the bloodstream resulting in hyperglycemia. However, if insulin levels are too high, this can lead to low sugar levels, or hypoglycemia.

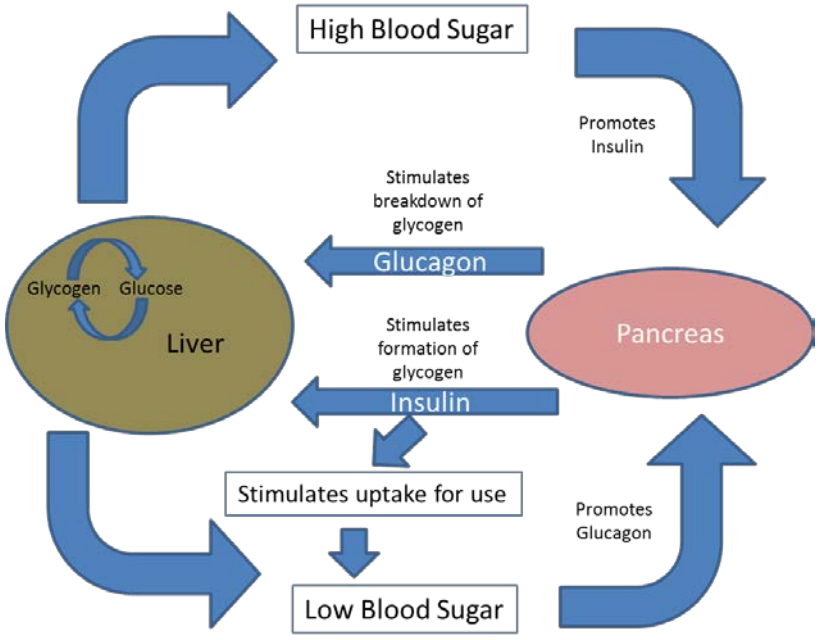

Figure 1. Insulin Production and Action[2]

While there are several sub-groups that fall under the "diabetes" heading, the two most common are type 1 and type 2.[2–4]

Clinical diagnosis of diabetes is often driven by the development of complications, acute or chronic. Most patients with T1D present with symptoms of hyperglycemia such as, polydipsia, polyuria, polyphagia, blurred vision, sudden weight loss, and some ketoacidosis. The American Diabetes Association (ADA) diagnostic criteria for diabetes mellitus consists of one of the following: a blood hemoglobin A1c (HbA1c) measurement of ≥6.5%, fasting plasma blood glucose measurements ≥126 mg/dL (7.0 mmol/L), a two-hour plasma glucose level ≥200mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT) (consumption of 75 g of glucose after an overnight fast), or a random plasma glucose of ≥200 mg/dL (11.1 mmol/L) in a person with symptoms of hyper- or hyperglycemic crisis.[4,5]

2.1.1 Classification and Epidemiology of Diabetes

The first guideline for diagnosis and classification of diabetes was published by the World Health Organization (WHO) in 1965. These guidelines are reviewed periodically, with the latest review having occurred in 1998.[6] The WHO currently recognizes two main classes of diabetes, type 1 and type 2. Gestational diabetes and a category referred to as "other specific types" are also recognized, but are less common.

Type 1 Diabetes

Type 1 diabetes (T1D) has previously been called insulin-dependent diabetes mellitus (IDDM), because it results from autoimmune destruction of the insulin-producing beta cells (β-cells) of the pancreas leaving the patient dependent on insulin injections for glucose control and survival[3]. While the exact cause of T1D remains unknown, it is believed that it is the result of a combination of autoimmune, environmental, and genetic factors[7]. The destruction of β-cells may eventually lead to a total loss of insulin production, which renders insulin dependent cells unable to properly metabolize glucose resulting in hyperglycemia. This excess glucose is then passed out of the body in urine.[8] T1D patients are usually diagnosed at younger ages, but it continues to present at all ages.

T1D accounts for approximately 5-10% of diabetes in the United States.[9] The SEARCH for Diabetes in Youth Study has estimated the incidence of T1D to be 19.0/100,000 with the highest incidence occurring in non-Hispanic whites and those aged 10 -14 years[10] . More African-American youth present with diabetic ketoacidosis at onset than Caucasians (27.9% versus 21.8%) and they also have significantly worse glycemic control at every age group. However, poor glycemic control is associated with age in both races, as older youth have poorer

control than younger.[11] T1D is most commonly diagnosed in children and youth, but can present at any age.

Type 2 Diabetes

Type 2 diabetes (T2D) is usually characterized by defects in insulin secretion along with insulin resistance in cells.[4] In these patients, the ability to produce insulin does not completely disappear, but they instead become increasingly insulin deficient and/or resistant which also results in hyperglycemia. The disease presentation may range from predominantly insulin resistance with some loss of insulin production, to predominant loss of insulin secretion with some or no insulin resistance.[3] Type 2 diabetes is typically found to be associated with obesity, diet, and physical inactivity.[8]

T2D is typically not diagnosed until the development of complications; up to one-fourth of all people with T2D may be undiagnosed. T2D is typically diagnosed after age 40, but is increasingly being diagnosed at younger ages. From 2002-2005 the rate of incident cases of T2D was 0.4/100,000 for youth under age 10, and 8.5/100,000 for youth over age 10. Rates of T2D are higher in US minority populations than in non-Hispanic whites. The rate of T1D was higher than the rate of T2D in non-Hispanic whites aged 10-19, but the Asian/Pacific Islander and American Indian youth populations had higher rates of T2D than T1D.[12] This study also found that African-American youth were more likely to be overweight/obese, have increased LDL cholesterol, high blood pressure, high depression symptoms, and poorer diets as compared to Caucasians.[11]

Gestational Diabetes

Gestational diabetes is general carbohydrate intolerance with onset of pregnancy that may result in high blood sugar levels and then usually resolves postpartum. Women who are at high risk for

this are older women, with history of glucose intolerance, history of large babies, from high-risk ethnic groups, as well as any woman with elevated fasting or random blood sugar levels.[3] Rates of gestational diabetes range from 2 – 10% of pregnancies, and 5-10% of women who have gestational diabetes are diagnosed with diabetes postpartum, the majority being T2D. Additionally, women who have had gestational diabetes have a 35-60% chance of developing diabetes in the next 10-20 years.[13]

Other Specific Types

Table 1 presents several of the other "specific types" of diabetes currently recognized by the WHO.

Table 1. Listing of the WHO diabetes etiological classification group "other specific types." [3]

Genetic defects of β-cell function	Genetic defects in insulin action	Diseases of the exocrine pancreas	Endocrinopathies	Drug or chemical induced	Infections	Immune mediated diabetes	Genetic Syndromes Associated with diabetes
Chromosome 20, HNF4α (MODY1)	Type A insulin resistance	Fibrocalculous pancreatopathy	Cushing's syndrome	Nicotinic acid	Congenital rubella	Insulin autoimmune syndrome	Down's syndrome
Chromosome 7, glucokinase (MODY2)	Leprechaunism	Pancreatitis	Acromegaly	Glucocorticoids	Cytomegalovirus	Anti-insulin receptor antibodies	Friedreich's ataxia
Chromosome 12, HNF1α (MODY3)	Rabson-Mendenhall syndrome	Trauma/ pancreatectomy	Phaeochromocytoma	Thyroid hormone		"Stiff Man" syndrome	Huntingtons's chorea
Chromosome 13, IPF-1 (MODY4)	Lipoatrophic diseases	Neoplasia	Glucagonoma	α-adrenergic agonists			Klinefelter's syndrome
Mitochondrial DNA 3243 mutation		Cystic fibrosis	Hyperthyroidism	B-adrenergic agonists			Lawrence-Moon-Biedel syndrome
		Haemochromatosis	Somatostatinoma	Thiazides			Myotonic dystrophy
				Dilantin			Porphyria
				Pentamidine			Prader-Willi syndrome
				Vacor			Wolfram's syndrome
				Interferon-α therapy			

Until the review in 1999, there was an additional category listed under the "other specific types," which consisted of diabetes mellitus presenting in undernourished populations. These were previously classified as "Malnutrition-related Diabetes" (MRDM) and consisted of two subtypes 1) fibrocalculous pancreatic diabetes (FCPD) and 2) protein-deficient pancreatic diabetes (PDPD or PDDM). However, the board decided that there was no convincing evidence that malnutrition could actually cause diabetes. Therefore, as of 1999, the MRDM class was removed from WHO classification. PDPD is now considered only to be a form of diabetes mellitus that is modified by malnutrition and FCPD has been reclassified as a disease (fibrocalculous pancreatopathy) that may potentially lead to the development of diabetes (see table 1).[3]

Differentiating between these classifications is difficult, as they present with many similar clinical features. Very few observational studies have been performed and therefore there are no clear-cut definitions for each. People within the same classification group may even present differently, further complicating the issue.

2.2 RATES OF DIABETES WORLDWIDE

In 2010 there were an estimated 285 million people with diabetes, including 6.6% of adults worldwide. While T2D accounts for 85-95% of all diabetes cases (possibly higher in low- and middle-income countries), T1D is the predominant form of the disease in children and adolescents.[2] An estimated 480, 000 children aged 14 and under are thought to have diabetes, with 77,000 new cases being diagnosed each year.[2,8] Geographic differences in rates can be seen in the results from the WHO DiaMond Study, an international registry system for patients with

T1D, which show a high variance in incidence. The rates range from <1/ 100,000 per year in South America and China to 49.9/100,000 in Finland.[14,15]

2.3 RATES IN DEVELOPING COUNTRIES – AFRICA

Understanding the burden of this disease is an important issue in developing countries as individuals here carry a disproportionate burden due to poverty and low access to health care. Yet it is in these countries that we know the least epidemiology. This is especially true on the African continent, which is comprised of the largest proportion of the world's developing countries (about 36%).[16]

It is estimated that in 2010 there were 12.1 million people with diabetes on this continent (about 4% of the world total), including 3.2% of the local adult population. This is expected to increase to 23.9 million by 2030, with the biggest increase in those aged 45 – 64 years.[2] These data, however, are extrapolated from a limited number of studies and these are often dated.

2.3.1 Type 1 Diabetes Epidemiology in Africa

It is especially important to know the rates of T1D in these populations, as these people will have more time to develop complications if they are not treated properly, and they may have fewer productive years of life.

Current estimates in Africa state that as of 2010, 35,700 children have type 1 diabetes, with 5,800 new cases diagnosed each year.[2] Compared to developed countries, the mean age of presentation in Africa is later[17–21] and in most countries there is a female preponderance.[17,22–25]

In Tunisia, however, there was no observed difference in sex,[26] while one study in Nigeria found higher rates in boys than girls.[27]

However, due to the paucity of epidemiologic studies in these countries, it is impossible to accurately estimate the true burden of disease. Type 1 incidence has been studied in five countries (Algeria, Tanzania, Tunisia, Libya, and Sudan) (table 2) and prevalence in only three (Sudan, Nigeria, Algeria) (table 3).[28]

Prevalence Studies

The prevalence of type 1 diabetes in school children (n=42,981 age 7 – 14 years) in Khartoum, Sudan was studied through use of a questionnaire.[23] From July – October 1987, males and females in grades 1, 4, and 6 from randomly selected schools, were given a survey with questions about diagnosed diabetes, current insulin use, and diabetes symptoms. Thirty-four previously known cases were identified as well as 7 additional new cases. There were a total of 41 cases resulting in a prevalence estimate of 0.95/1,000. In both sexes, prevalence increased with age and there were slightly more females than males in each age group, but the difference was not statistically significant. The prevalence rate was unexpectedly high and though this was a representative population (97% of school age children in Khartoum attend public elementary schools) it was possible that asymptomatic patients or those with no glucouria or ketonuria were missed. Additionally, the Northern Sudan populations are primarily of mixed Arab and Noba (black) decent, while the Southern population is ethnically pure African (black), possibly limiting the generalization of the results.[23]

Questionnaires were also given to Nigerian Igbo school children, aged 5 – 17years (n = 77,862), from three different school districts (Ezza, Ishielu, and Okaukwa) between June - August, 1990.[29] This survey asked questions on demographic data, history of diseases, recent

doctor visits, drugs being taken, and about the presence of diabetes symptoms (enuresis, polyuria, polydipsia, polyphagia, and weight loss) in either the participant or their siblings. Fourteen children reported previously diagnosed diabetes and 12 new cases were identified for a total of 26 cases and an overall prevalence rate of 0.33/1,000. Boys were found to have a higher prevalence (0.38/1,000) than girls (0.25/1,000) and peak prevalence was found in those aged 14 – 17 (0.74/1,000). The higher rate in boys could be explained by fewer girls being registered in schools or worse survival of females due to the beliefs of the Igbo tribe that girls are the inferior sex. It is additionally difficult to expand the prevalence rate from this study to the entire Nigerian country because it focuses on only one tribe that differs from other regional tribes in lifestyle, economic class, and diet.[29]

A Type 1 diabetes registry in the Department (Province) of Oran, Algeria was used to identify all adolescent cases of diabetes in those aged less than 20 years (by December 31st, 1988), with diagnosis of disease before age 15.[30] Ascertainment rates of this registry were cross compared with the results of a questionnaire sent to local practitioners, and the results were highly correlated. Registry data from 1979 to 1988 was used and a total of 173 families were further examined. They determined a prevalence rate of 0.27/1,000 in this population. While ascertainment was indeed high applying the prevalence for a specific province to the entire country may not be representative of Algeria as a whole.[30]

Table 2. Prevalence estimates (per 100,000) of type 1 diabetes in African Countries.[23,29,30]

Country	Study Year(s)	Age of Population	# of Cases	Prevalence/ 100,000
Sudan	1987	7 - 14	41	95
Nigeria	1990	5 - 17	26	33
Algeria	1979 - 1988	0 - 15	173	27

Incidence Studies

Examination of the same registry data in Oran, Algeria also allowed investigators to estimate the annual incidence of diabetes. The annual incidence had a mean of 4.4/100,000 new cases per year. The incidence increased at a steady rate from 1.6/100,000 in 1981 to 8.1/100,000 in 1988, suggesting that the burden of this disease is indeed increasing with time. It is, however, impossible to know for certain if this is a true increase in disease rates or if it is an increase in disease awareness and detection.[30]

Registry data was also used to estimate the incidence of diabetes in Dar es Salaam, Tanzania.[31] Data collected at the main hospital in the country, Muhimbili Medical Center, from January 1, 1982 to December 31, 1991 was used to identify 86 children between the ages 0 -19, who were diagnosed with diabetes during this time. There were slightly more males (n = 45) than females (n = 41) and only one patient that was diagnosed <5 years. The average annual incidence over this time period was 1.5/100,000 (range = 1.3 – 1.7/100,000) and incidence increased with age, with the highest rate seen in children ages 15 – 19 (3.4/100,000). Because most patients diagnosed with diabetes are cared for at this hospital, the authors believed that case identification was as complete as possible. However, it is still possible that children may have died before their diabetes was diagnosed, leading to an under-estimation of the actual incidence rate.[31]

In Tunisia, another incidence study was performed using data from WHO DIAMOND registries in three randomly selected districts (Beja, Monastir, and Gafsa).[26] The study ran from Jan 1, 1990 to Dec 31, 1994 and 156 incident cases in children under the age of 20 were identified (79 male, 77 female). The average age at diagnosis was 11.18 ± 4.69, with a peak in incidence for those 10 – 14 years. The observed standardized overall incidence rate was 6.95/100,000. Case ascertainment employed the capture-recapture method, and since all patients in these districts with diabetes are required to visit local outpatient offices for insulin, it is not likely that many cases were missed. The use of registry data also helped to ensure that all known cases were included in the analysis. However, it is still possible that there were un- or misdiagnosed cases that were not included.[26]

WHO DIAMOND registry data were also used in Libya to look at the incidence of type 1 diabetes.[32] They used registry data from the city of Benghazi and identified 276 new cases between the ages of 0 – 14 years who were diagnosed between January 1, 1991 and December 31, 2000. This resulted in an overall incidence rate of 8.3/100,000, which is higher than the previously estimated incidence of 7.0/100,000 collected from 1981 to 1990. They saw a significantly ($p < 0.001$) different rate of incidence between females (9.1/100,000) and males (6.6/100,000), and an increase in incidence with age in both sexes until they peaked in those aged 10 – 14 years. Case ascertainment was mainly from records from the main diabetes clinic or from the local children's hospital, and some discharge files from five additional area hospitals and 10 polyclinics were also used. The physicians in this city have a high awareness of diabetes, and there is a resident medical school with adequate access to diagnostic tools and management options. It is, therefore, believed that there are not many undiagnosed cases in the Benghazi area.

However, these assumptions may not be applicable to rural areas of this country thus the generalizability of these results to the rest of the country may not be high.[32]

Incidence of type 1 diabetes in Sudan was estimated using the results of an ongoing registry from 1987 – 1990.[22] Children that were eligible for this study were under the age of 15, living in Khartoum and had developed diabetes within the study time period. A total of 327 cases were reported over the four years, with 95% case ascertainment with the capture-recapture method. Over the time span of this study, the investigators saw a dramatic increase in incidence from 5.9/100,000 in 1987 to 10.1/100,000 in 1990, with the highest rates seen in children aged 10 – 14 years. Though they saw a 76% increase in incidence, they believe that the incidence rate for 1987 was likely an underestimate as it was the first year the registry was in effect. It was also possible they missed children that were treated in private clinics and those who died before diagnosis, as it was common for children that presented with comas to first be treated for cerebral malaria or meningitis.[22]

Table 3. Results of estimates of incidence rates (per 100,000) of type 1 diabetes in African Countries.[22,26,30–32]

Country	Study Year(s)	Age of Population	# of Cases	Incidence/ 100,000
Sudan	1987 - 1990	0 - 15	327	10.1
Tunisia	1990 1994	0 - 19	156	6.95
Libya	1991 - 2000	0 - 14	276	8.3
Tanzania	1982 - 1991	0 - 19	86	1.5
Algeria	1979 - 1988	0 - 15	173	4.4

Each of the previous studies has their own strengths and weaknesses, with the biggest weakness being generalizability. The results of these studies may all be underestimates of the

true disease burden due to misdiagnosis, which has been reported to be high in this region,[33] and death before diagnosis. Many cases may be missed due to death before diagnosis because of lack of diagnostic tools and decreased physician awareness. Several of the afore mentioned studies that used population surveys were able to identify new cases of diabetes in persons who were previously healthy and were living 'normally' with their disease unnoticed, thus supporting the idea that cases are indeed going undiagnosed.[23,29] These previously unidentified cases highlight an ongoing debate in Africa: the difficulties of diagnosing and classifying types for this disease.

2.4 DIABETES CLASSIFICATION IN AFRICA

Intermediate forms of diabetes have been previously described in adolescent patients in Africa and span a wide variety of ketosis presentation and insulin requirement.[34] There are reports of patients discontinuing their insulin, but who seldom develop ketoacidosis. These cases were previously placed under the classification of MRDM and also referred to as 'tropical diabetes.'[35] Diagnosis for MRDM was based on: detection before age 30, history of weight loss and malnutrition, hyperglycemia and lack of ketosis (in most cases). Those diagnosed with the FCPD subtype of MRDM have calculi which can be assessed with abdominal radiography, and abnormal exocrine pancreatic function.[36] It was previously suggested that diets based heavily on cassava consumption could potentially lead to the development of FCPD. It was thought the cyanogenic glucosides in the cassava root might be toxic to the pancreas, but a study by Swai et al, showed that higher exposure to dietary cyanide does not increase the prevalence of diabetes in Tanzania.[37] Following a review of this and other similar studies by a WHO sponsored international workshop, it was decided that though malnutrition may exacerbate or change the expression of other types of diabetes there is no convincing evidence that it can actually cause

diabetes. Because the WHO no longer recognizes this category it has become a topic of debate as to how to properly classify patients in Africa properly.

The WHO classification system before 1999 which was based on clinical factors and therapy has become outdated as rates of obesity increase and insulin is used more frequently as therapy regardless of diabetes type. The current system, therefore, focuses more on the etiologic and physiologic aspects of the disease. While this provides several benefits, it also introduces additional challenges as it does not yet have specific definitions for each of the types of diabetes and assumes that there is no overlap between the two main categories of type 1 and 2. To attempt to better characterize the etiology of the disease to define classification groups, autoimmunity, insulin sensitivity, and genetic risk are being examined.

The most commonly used markers for autoimmunity are: islet cell antibodies (ICA), insulin antibodies, insulinoma-associated-2 antibodies (IA2A), and glutamic acid decarboxylase antibodies (GADA). β- cells are just one type of islet cell, and GAD is a protein that is also made by the β- cells. Zinc transporter 8 (ZnT8), an islet β- cell secretory granule membrane protein, has also been identified as an autoantibody antigen in type 1 diabetics.[38] It is believed that these autoantibodies lead to the destruction of β-cells by the individuals own T-cells.
Levels of C-peptides, which are produced in the same amount as insulin, are also often measured as a marker for insulin production. Insulin sensitivity is often measured through hyperinsulinemic-euglycemic clamps, but can also be estimated through the use of previously validated equations.[39,40] Those patients with type 1 are typically autoimmune, ketosis prone, and insulin sensitive, while those with type 2 are non-autoimmune, rarely present with ketosis and have insulin resistance.[39]

A recent study from the American SEARCH for Diabetes in Youth group, found that when looking at autoimmunity and insulin sensitivity in patients under age 20 (n=2,291), the majority of the subjects fell into either the typical type 1 (autoimmune with insulin sensitivity, 54.5%) or type 2 (non-auto immune and insulin resistant, 15.9%) categories.[41] However, there were several that were classified in the other two non-traditional categories of autoimmune and insulin resistant or nonautoimmune plus insulin sensitivity, which suggests that even in the western world, the current classification system is limited.

The accurate measurement of islet auto antibodies is notoriously difficult in non-research labs. Of the few studies performed in Africa, the prevalence of ICA in type 1 diabetic patients is highly variable. Low prevalence has been found in Tanzanians[42] (8.6%) and Nigerians[43] (10%) and higher amounts were seen in Ethiopians[44] (43%) and South African Blacks[45] (39.4%). High levels of GADA have also been found in South African Blacks, thus further supporting an immunological etiology.[46]

A more recent etiological study in Ethiopia, however, supports the need for further studies in Africa. Of 69 patients being treated with insulin, only 42 (61%) were C-peptide-negative and 35% were GADA-positive. An additional 38 (36%) had immunological or C-peptide results that were inconsistent with the current classification system. These results, along with the high levels of malnutrition have led the authors to suggest that the inclusion of malnutrition-diabetes be re-evaluated.[47]

Genes have long been thought to play a role in the development of T1D, as it seems to run in families. The genes responsible for coding the human leukocyte antigens (HLA) have been identified as genes that may predispose a person to developing T1D. These antigens may incorrectly identify β-cells as being foreign, leading to autoimmunity. Of the diabetic patients

living in the western world, over 90% of those with type 1 diabetes have one or both of the HLA-DR3 or HLA-DR4 haplotypes.[48]

Previous studies of class 1 antigens (HLA-A,B and C) in South Africa and Nigeria have shown significant associations with HLA-B8, B14, and B8/14, as well as a negative association with BW42. [19,49] Other studies on class II antigens (HLA-D, DR) have shown a positive association with HLA-DR4.[19] Allele-specific tests have allowed identification of several HLA class II alleles in South African Zulu,[50] as well as several point mutations (*CTLA4* in Ghana and *TLR3* in South African Zulu).[51,52]

2.5 OVERVIEW AND EPIDEMIOLOGY OF COMPLICATIONS

No matter what the etiology, uncontrolled glucose levels can lead to the development of complications. Acute complications include diabetic ketoacidosis and severe hypoglycemia, while chronic complications are classified as microvascular (neuropathies, nephropathy, or retinopathy) or macrovascular (atherosclerotic conditions: coronary artery disease, peripheral vascular disease, and cerebrovascular disease). The presence of one or a combination of several of these complications may lead to the most severe outcome – premature death.

2.5.1 Acute

Ketoacidosis

A “normal” person with insufficient levels of glucose available will start to break down fat into ketones for use as an alternative energy source. Diabetic patients who have insufficient amounts insulin, may have elevated ketone levels because their bodies cannot utilize glucose as an energy

source. As the levels of ketones in the blood rise, the pH level drops in the patient, and the body tries to reduce the levels by expelling the ketones in urine or through the lungs. If the pH drops too low, the person can develop ketoacidosis (DKA), which is considered to be a medical emergency and can lead to coma and death. Ketoacidosis may occur at the onset of disease or if not enough insulin is being provided in therapy.[8] The SEARCH study in the US found that 1 in 4 diabetic children (both type 1 and type 2) presented with DKA at diagnosis. The prevalence decreased with age and was higher in those with type 1 diabetes than those with type 2.[53] Race does not seem to have an effect on development of ketoacidosis,[54] but adolescent girls are more likely to develop DKA than boys.[55] In Addis Ababa, Ethiopia, a prospective study following 431 diabetic patients from 1976 to 1990 found that 11% of patients presented with DKA at diagnosis and 38% (n=164) had at least one episode of ketoacidosis during follow up.[56] An earlier study from Ethiopia found similar results (36.8% had at least one episode during follow up).[21] In Tanzania, 75% (n=75) of children ages 5-18 years attending a diabetes clinic in Dar es Salaam (n=99) presented with DKA at diagnosis, while 89.9% had experienced at least one previous episode.[57] A lower prevalence of DKA on admission was seen in an additional study from Tanzania where 23% presented upon diagnosis.[58]

Severe Hypoglycemia

Hypoglycemia is the leading limitation in the management of both type1 and type 2 diabetes. When a patient's glucose level falls below 70 mg/dL, they may begin to feel symptoms which include dizziness, weakness, and confusion. If glucose levels fall below 55 mg/dL(severe hypoglycemia) the patient will often lose consciousness, and levels below 20mg/dL can also trigger seizures. Patients may show symptoms of hypoglycemia an average of twice per week, and 10-25% of patients with type 1 diabetes experience at least one severe episode a year.[59] In

the DCCT 65% of patients with more intensive insulin control were reported to have suffered severe hypoglycemia over 6.5 years for follow up.[60] Internationally, 20-30% of primary school children and 15-20% of teenagers experienced one severe hypoglycemic episode with either unconsciousness or seizures within a one year period.[61] In Ethiopia, 10.2% (n=44) of patients had at least one severe hypoglycemic episode, three of whom died.[56] General symptoms of hypoglycemia were reported in 55.6% (n=55) of children in Dar es Salaam, Tanzania.[57]

2.5.2 Chronic

Neuropathy

There are two main classifications of neuropathies: peripheral and autonomic. Peripheral neuropathy (PDN) is nerve damage in the arms or legs, while autonomic neuropathy is a result of damage to the nerves of the autonomic system which regulate muscles of the heart, bladder, gut and other vital organs.[62] One specific type of autonomic neuropathy, cardiac autonomic neuropathy (CAN) is especially common in patients with type 1 diabetes. It is the result of damage to the autonomic nerves that innervate the heart and blood vessels and can cause abnormalities in heart rate and hemodynamics. This then may result in abnormal heart rate, tachycardia, intolerance to exercise and orthostatic hypertension.[63] Comparing rates of this disease can be difficult due to the differing strictness of definitions used for each study. However, neuropathy of some sort occurs in approximately 50% of patients with type 1 diabetes by 20 years of disease duration.[63] CAN was also reported in almost 39% of patients after 25 years of disease duration in the Pittsburgh Epidemiology of Diabetes Complication (EDC) study.[64] Rates of neuropathy in Addis Ababa, Ethiopia, have been reported at 10.4% (7.9% had PDN and 2.5% had CAN).[56] Significantly higher rates were seen in a small study from Soweto,

South Africa, where 35.3% (n=6) of patients with an average disease duration of 23 years had diagnosed neuropathy.[65]

Retinopathy

Diabetic retinopathy is the most common eye complication in diabetes.[66] Retinopathy is caused by damage to the blood vessels in the retina from chronic hyperglycemia. Non-proliferative retinopathy (NPDR) is the early stage of the disease and is marked by the formation of microaneurysms (weakened outpouches) in the blood vessels of the retina. Over time these may hemorrhage and other vessels become blocked. To compensate for this damage, weaker vessels are formed in the retina or even in the vitreous. These weak vessels tend to hemorrhage causing bleeding into the eye, obscuring vision. This more advanced stage is referred to as proliferative diabetic retinopathy (PDR). Eventually, this damage may lead to blindness.[67] Data from the National Health and Nutrition Examination Survey (NHANES) report the prevalence of diabetic retinopathy to be 28.5% among adults with diabetes in the US. It is slightly more common in men than women and non-Hispanic blacks have a higher rate than non-Hispanic whites.[66] The Pittsburgh EDC study showed that almost 100% of their type 1 diabetic participants had developed retinopathy by 20 years duration, detected by fundus photography.[68] The major risk factors for retinopathy seem to be male sex, higher HbA1c levels, longer duration, and higher systolic blood pressure.[66] Reports from Africa range from 9.5% of type 1 diabetes patients in Ethiopia[56] to 58.8% in Soweto, South Africa.[65] A study in Dar es Salaam, specifically focusing on children ages 5-18, reported that 22.2% of their cohort had prevalent retinopathy.[57]

Nephropathy

Diabetic nephropathy is caused by prolonged damage to the capillaries of the kidneys and is most likely a result of metabolic dysfunction associated with chronic hyperglycemia, insulin

resistance and genetic susceptibility.[69–71] Development of this disease starts with a thickening of the glomerulus of the kidney and as it becomes more damaged, more and larger proteins are filtered out in the urine. The first stage of diabetic nephropathy is called microalbuminuria and is a result of increased levels (30-299 μg/mg) of serum protein (albumin) being excreted in urine. As the disease progresses, the concentration of albumin in the urine increases (≥300μg/mg), resulting in overt nephropathy (ON) and eventually in complete failure of the kidneys and End Stage Renal Disease (ESRD).[5,69] Major predictors of nephropathy are disease duration, glycemic control, dyslipidemia and the presence of hypertension.[72] Diabetic nephropathy is seen in 3.3% of the US population and 20-40% of all patients with diabetes.[5,73] It is the single leading cause of ESRD.[5] Though the prevalence of type 1 diabetes is lower, almost 50% of all ESRD cases are in patients with this disease.[74] Additionally, 29% of type 1 diabetes patients develop microalbuminuria with in the first 20 years of developing diabetes.[75] Two studies from Dar es Salaam, Tanzania report the presence of microalbuminuria in 29.3% of children aged 5-18 with average duration of 4.76 years,[57] and 12% of patients with average age of 21 and disease duration of 3 years.[76] Similar results were seen in Soweto, South Africa (11.8%),[65] while a slightly lower percentage (6.0%) was seen in Addis Ababa.[56]

Cardiovascular diseases

Most macrovascular complications of diabetes come as a result of the development of atherosclerosis. Atherosclerosis is a progressive process in which the artery walls thicken from build-up of plaques. Plaques are formed when oxidized LDL damages the vessel walls and the body responds with white blood cells which absorb the LDL forming foam cells. These cells are unable to process the oxidized LDL and thus grow larger and then breakdown forming cholesterol rich plaques, which further activates the body's response. These plaques, which also

reduce the diameter of the vessel, impede the flow of blood. If the plaques rupture, a clot may form and they may locally block blood flow or break off and travel to other areas and cause tissue damage or death there. The three most common complications of this process seen in diabetics are coronary artery disease, peripheral vascular disease and cerebrovascular disease.

Coronary artery disease

Coronary artery disease (CAD) is the development of atherosclerosis in the small vessels that supply the heart with blood. The major complication of this disease comes when the plaque ruptures causing a block in the vessel, depriving the local heart muscle of oxygen. This may cause damage to the tissue or tissue death. This may result in an immediate heart attack, or in later heart failure due to weakened muscles from oxygen deprivation. The relationship between hyperglycemia and CAD is not well understood. A few reports show that poor glycemic control can predict CAD,[77] while most other studies have shown either a weak or no association.[78,79] However, change in glucose control in the absence of renal disease has since been found to predict CAD.[77,80,81] CAD is currently the leading cause of diabetes related deaths in the US.[82] People with T1D are at a 10-fold increased risk of developing CAD than the general population.[83]

Peripheral vascular disease

Peripheral vascular disease (PVD) is the development of any atherosclerotic plaques in any areas other than the heart or brain. Reduction of blood flow to the legs and feet is commonly seen in diabetic patients and may lead to foot ulcers, gangrene, and in the most severe case –limb amputation. The most common predictors are disease duration, LDL cholesterol, heart rate, estimated glucose disposal rate, nephropathy, retinopathy, glycemic control, and low ankle brachial index.[84] Hospital discharge data report that 45% of all amputations in the US are for

patients with diabetes. Patients with diabetes are at 15 times higher risk of amputation than those who do not.[85] In the EDC study, 27% of patients with at least 25 years duration, reported PVD, with females having increased risk.[84]

Cerebrovascular disease

Cerebrovascular disease is caused by the presence of atherosclerosis in the vessels of the brain. If blood flow to the brain is interrupted, the un-oxygenated tissue will be damaged, or possibly die. This condition is also known as a stroke. Ischemic strokes occur when the blood supply is cut off due to a blockage (such as a dislodged clot from elsewhere in the body), while hemorrhagic strokes occur when a weaker vessel ruptures. Thrombotic strokes are a result of a clot that actually forms within the brain. Women with diabetes have been reported to have a 6-fold increased risk of ischemic stroke than those without diabetes.[86]

There are currently no reports on the prevalence of these macrovascular complications in type 1 diabetic patients in Africa. This is due mainly to the high level of out of hospital mortality related to these complications, lack of death certificates with proper cause of death recording, lack of diagnostic facilities, or death from acute complications and renal disease before CAD can develop.

2.5.3 Mortality

Patients with T1D are at increased risk of death as compared to the general population.[87] Mortality due to diabetes has been studied internationally by the Diabetes Epidemiology Research International Study (DERI). This study found increased mortality in the US as compared to Finland, Israel, and Japan.[88] As disease duration increases, cause of death shifts from primarily due to acute complications within the first 10 years, to chronic complications

after 20 years duration.[87] In Africa, 1 in 20 deaths for those aged 20-79 years is due to some form of diabetes. In total, it is estimated that there were over 330,000 deaths from all types of diabetes in this region.[2]

There have been relatively few studies in Africa that look at the mortality rates of children with T1D. As study of the effects of healthcare differences in Mozambique and Zambia examined how location (urban versus rural), variations and inequalities of care, availability of diagnostic tools and availability of insulin affected mortality. The life expectancy of a child with T1D living in rural Mozambique is estimated to be less than a year (0.6 years), 2.1 years in urban cities, and 3.8 in the capital city. For children >15 years, the estimated life expectancy is 2.9 years in rural areas, 11.1 years for urban, and 20 years in the capital. In rural Zambia, life expectancy for children ages 0 – 14 years was 9.0 years in rural areas, 13.0 years in urban areas, and 18.0 years in the capital city. For children >15 years, the estimated life expectancy of a child living in a rural area is 14.0 years, 19.0 years for urban areas, and 27.0 years in the capital city.[89] A cohort of 88 T1D patients in Soweto, South Africa was followed for 20 years from 1982 to 2002. By 2002, 21 patients had died, 28 were still alive, and 39 were lost to follow-up. They excluded those on whom they did not have complete data, and calculated a mortality rate of 43% (21/49), but due to the large number that were censored, they used Kaplan – Meier plots to calculate a hazard ratio (H) of 0.33 (20- year mortality risk). The mean duration of disease at time of death was 23 years and the average age at death was 33 (range 22 – 46) years. The most common cause of death was chronic renal failure (n = 9, 42.8%), and 6 (28.6%) died from hypoglycemia, 2 (9.5%) from acute infection, 2 (9.5%) from ketoacidosis, and 2 (9.5%) from unknown causes.[65]

Of 431 T1D patients in Addis Ababa, Ethiopia, 42 (9.7%) members of the cohort had died after 15 years of follow up (mean duration of disease at death of 9.2 ± 1.9 years). Acute complications of diabetes were the most common cause of death with 7 due to ketoacidosis, 3 to infections, and 3 to hypoglycemia. Six other patients died due to complications of nephropathy, 5 to septicemia secondary to another infection, 3 due to gangrene, 3 due to tuberculosis, 1 due to stroke, and 11 others died due to miscellaneous or unknown causes. Survival at 5 years was 96%, at 15 years 82%, and at 20 years 63%.[56]

In Dar es Salaam, 5 year survival for a cohort of 272 patients was 71% when all known deaths were accounted for and 60% when all known and probable were included. Twelve patients died (32%) due to infection, 3 (8%) due to DKA, 2 (5%) due to hypoglycemia, and 4 (11%) due to unknown causes.[58]

2.5.4 Prevention of Complications

The Diabetes Control and Complications Trial (DCCT) has demonstrated that maintaining a blood glucose level as close to the normal range as possible (goal of HbA1c <7%) reduces or delays the risk of developing long-term micro- and macro-vascular complications. The results of the DCCT showed a 76% decrease in risk of retinopathy, 60% less neuropathy, and 35-60% less kidney damage in those with tighter control.[60] They also demonstrated that intensive treatment reduced the risk of any cardiovascular disease by 42% and the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease by 57%. However, they also showed that there was an increased risk of hypoglycemia in the tight control group, thus implying that tight control is not without risk.

Risk factors for each of the following complications also need to be monitored carefully to adequately prevent complications.

Hypertension/blood pressure

Blood pressure (BP) should be measured at each clinical visit as BPs over 115/75 mmHg are associated with increased cardiovascular events and mortality in people with diabetes.[90] Each individual should have appropriate goals based on their age, therapy and treatment, but a systolic BP of <130 mmHg and a diastolic BP of <80mmHg are recommended. Usual treatment includes lifestyle modification and pharmacologic therapy of antihypertensives.[5]

Dyslipidemia

Dyslipidemia is more common in patients with diabetes (especially those with type 2 diabetes) and should be monitored as risk of cardiovascular events can be prevented through controlling these factors. Lifestyle modification and statin therapy are the two most common treatment methods. Presence of cardiovascular disease, age, and response to other treatment options are considered when choosing the best treatment option.[5]

2.6 MANAGEMENT OF DIABETES

To prevent complications adequate management of glucose levels is necessary. Ideally, diabetes management should be provided by a well-coordinated team of physicians, nurses, dieticians, pharmacists, and mental health professionals. Upon diagnosis a patient should also be provided with a detailed examination (table 4), so that the most effective management program may be designed. The family of the patient should be involved, but diabetes self-management education (DSME) should be the focus of the approach. DSME is:

> "the ongoing process of facilitating the knowledge, skill, and ability necessary for diabetes self-care. This process incorporates the needs, goals, and life experiences of the person with diabetes. The overall objectives of DSME are to support informed decision-making, self-care behaviors, problem-solving, and active collaboration with the health care team to improve clinical outcomes, health status and quality life in a cost-effective manner." [5,91]

The age, daily schedule, physical activity level, diet, social situation, culture, and presence of complications for the patient should all be taken into consideration when designing specific treatment plans. All treatment regimens, however, should have the same goal: good blood glucose control.[5]

Table 4. Components of a comprehensive diabetes examination.[5]

Medical History • Age and characteristics of onset of diabetes • Diet, physical activity, nutritional status, weight history, growth and development • Diabetes education history • Review of previous treatments and response to therapy • Current treatment (medications, diet, physical activity, results of glucose monitoring and ability to adjust accordingly) • Diabetic Ketoacidosis frequency, severity, and cause • Hypoglycemic episodes (awareness, frequency and cause) • History of diabetes related complications (Microvascular: retinopathy, nephropathy, neuropathy; Macrovascular: CHD, cerebrovascular disease PAD); psychosocial problems; dental disease)
Physical Examination • Height, weight, BMI • Blood pressure • Fundoscopic examination • Thyroid palpation • Skin examination • Foot examination
Laboratory Evaluation • HbA1c • Fasting Lipid profile (total, LDL and HDL cholesterol and triglicerides) • Liver function tests • Urine albumin excretion or urine albumin to creatinine ratio (A/C ratio) • Serum creatinine and calculated GFR • Thyroid-stimulating hormone (in type 1 diabetics, dyslipidemia or women over 50 years)
Referrals • Dilated eye exam • Family planning for women of reproductive age • Registered dietician for medical nutrition therapy (MNT) • DSME • Dental examination • Mental health professional

There are two standard ways of monitoring glucose control: 1) patient self-monitoring of blood glucose (SMBG) and 2) hemoglobin A1c (HbA1c). The timing and number of SMBG depends on the particular needs and goals for the patient. Patients using multiple insulin injections are recommended to monitor at least three times per day, but for patients at higher risk

for hypoglycemia more tests may be needed. It is very important that patients using this method of control be educated in how to properly use their glucose meter, know when to test, and how to adjust their diet, exercise, insulin or other treatment options accordingly. Individual glucose targets will vary by patient and timing of the test,[5] but table 5 shows a summary of the ADA recommendations.

Table 5. Summary of glycemic goals for specific age groups.[5]

Age Range (years)	Pre-prandial goal (mg/dL)	Peak post-prandial goal (mg/dL)	Bedtime/ Overnight (mg/dL)	HbA1c (%)
0 – 6	100-180	-	110-200	<8.5
6 – 12	90 -180	-	100-180	<8
13 – 19	90-130	-	90-150	<7.5
19+	70-130	<180	-	<7.0

Another way to assess glucose control is through measuring glycated hemoglobin (HbA1c). Hemoglobin is the major protein in red blood cells and its main function is to transport oxygen in the blood stream. When glucose is present in the blood stream, it causes a glycation, of the hemoglobin molecules. The levels of glycated hemoglobin can then be used as a measure of the average glucose levels. Since red blood cells, and thus their hemoglobin molecules, are present in the blood stream for up to 90 days, this measurement can present a 'snap shot' of the average glucose levels of a person for the last 3 months.[4] Results of the Diabetes Control and Complications Trial (DCCT) showed that patients who reached the goal of a HbA1c level <7% had much better outcomes, and therefore most physicians use this as a general goal for their patients.[81] However, for children acceptable HbA1cs are slightly higher to reduce the risk of hypoglycemia. It is recommended that HbA1c tests be performed quarterly in patients who are not meeting glycemic goals or whose therapy has changed, but patients who are meeting goals

and are under consistent therapy need only two tests per year.[5] There are several limitations to this test, however. Patients with conditions that affect their red blood cells (hemolysis or those with hemoglobin variants) or those with high blood loss or anemia may have HbA1c measures that do not accurately reflect their control. Also, as this test provides a picture of average control, it does not accurately reflect glycemic variability within a patient. Therefore, a combination of both glucose monitoring methods may be the best option.[5]

2.6.1 Specific Therapy Approaches

Type 1 diabetes

For those diagnosed with T1D, insulin therapy is essential for survival and to reach glycemic goals. There are currently several types of insulin available, each with a different time course of action. When insulin is normally secreted by the pancreas, hexamers are formed by the binding of six individual insulin molecules. These hexamers must be broken down into dimers and monomers before they can enter the bloodstream. Scientists have found ways to manipulate this characteristic as well as combining additional products to control the action time of injected insulin.[8]

Rapid acting insulin (Lispro, Humalog, NovoRapid/NovoLog, Apidra) was developed in such a way that hexamer formation is greatly reduced, resulting in absorption within 5-10 minutes, with peak action at 1 hour. Short-acting insulins (Actrapid, Humulin Regular S, Insuman Rapid) have the same molecular structure as those secreted from the pancreas and begin to work 20 -30 minutes after injection with a peak at 1.5 – 2 hours. The effects can last for up to 5 hours.[8]

In people without diabetes, there is always a low level of insulin in the blood to cover the glucose that is released from the liver between meals. This is known as basal or background insulin. Ideally, an insulin regimen should mimic the profile of a non-diabetic person's natural response to prevent hyperglycemia and avoid hypoglycemia. Therefore basal insulin injections are also given to diabetic patients. These insulins are either intermediate-acting or long-acting.[8] There are two intermediate-acting insulins (NPH and lente). The action of NPH insulins is prolonged by adding protamine to short-acting insulin molecules. NPH insulin (Insulatard, Humulin I, Insuman Basal) will work after about 2 – 4 hours and last up to 8 or 9 hours. Lente insulins are prolonged by using excess free zinc to cause the binding of insulin monomers into lager crystals. These insulins (Monotard, Humutard) peak at 4 – 5 hours. A newer intermediate-acting insulin, NPL, increases its effect time by adding protamine (like NPH). However if this is mixed with Humalog, it remains stable for at least one year.[8]

The older long-acting insulins (Ultratard, Humulin Zn) started to work 2-4 hours post injection and lasted up to 24 hours, with a peak at 6-12 hours. However, in 2000 Lantus (glargine) was developed to provide better 24 hours basal coverage, by actually altering the insulin molecule itself. This causes the insulin to have a more even level of coverage over the 24 hours, more closely mimicking the body's natural secretions. Levemir (detemir) was then introduced in 2004, and its action and results are similar to those of Lantus (glargine).[8]

The DCCT showed that intensive insulin therapy (three or more insulin injections per day or continuous subcutaneous insulin infusion) in patients with type 1 diabetes improved blood glucose levels and decreased complication rates. However, it was also found that the intensive treatment increased the rate of severe hypoglycemia.[81] It is therefore recommended that patients use multiple injections a day of basal and prandial (meal coverage) insulin, choose doses of

insulin based on carbohydrate intake at meals and predicted physical activity, and use newer insulin analogs. It is also important that patients with type 1 diabetes also be screened for additional autoimmune diseases such as thyroid dysfunctions, vitamin B12 dysfunctions and celiacs disease if they have any symptoms.

Type 2 diabetes

T2D patients usually require oral medication therapy to aid with their diabetes control. The three established types of these drugs are those that increase insulin production, those that improve insulin sensitivity, and those that delay absorption of carbohydrates from the blood. There are several different drugs in each of these categories and the physician uses the patient's symptoms and contraindications to decide which drug is most appropriate.

Additional medical nutrition therapy (MNT) should be provided. For obese patients, a calorie, carbohydrate and fat restricted diet should be followed. Increased physical activity should also be included in the treatment regimens, as weight loss has been shown to reduce insulin resistance.[4,5] In patients who present with weight loss or severe hyperglycemia, insulin may be prescribed.[5]

2.7 DIABETES MANAGEMENT IN AFRICA

In order to have the most effective treatment for diabetes, a patient must have access to proper diagnostic and monitoring techniques as well as to treatment options. However, in developing countries, many of the people affected by this disease will not have access to these necessary tools. In Mozambique only 18% of health care facilities have the ability to measure blood glucose levels and only 8% can test for urinary ketones (additional marker of diabetes).[89] Beran and Yudkin describe the health care situation in Africa as such:

> "In most developing countries the main barriers to chronic disease control are inadequate financing and availability of staff … a dearth of information about disease burden and management, and the present orientation of health systems toward acute care." [92]

Due to the history of focusing on communicable diseases in this region, most health care systems are geared towards treating diseases with shorter natural histories. They are not used to long term follow up and continuity of care across several specializations.[93] In one report ranking 191 countries by the overall performance of their health systems, 80% of African countries were in the fourth and fifth quintile and only one (Morocco) was in the top quintile.[94]

Health care in these countries also tends to be concentrated in the larger urban areas, which is usually too far from those in rural areas who often need assistance the most. Very few countries in Africa have had official health care assessments, especially specific to diabetes care, but for those who have, the most frequent findings have been: low patient attendance, consult time is too short to provide accurate patient education, insufficient staff, untrained staff, complications of diabetes are not properly (or often at all) monitored, glucose and blood pressure are in poor control, referral systems are lacking, and record keeping is very poor.[95–101]

Diabetes prevention (specifically for T2D) is practically non-existent in this region. As urbanization occurs and obesity rates rise, primary prevention through education will become increasingly necessary. Mass-media may become a useful means of providing education quickly to the people through commercials and soap-opera type shows.[102]

The most pressing issue, however, is the lack of insulin availability to this region. A global survey by the International Diabetes Federation's (IDF) Task Force on Insulin, Test Strips, and Other Diabetes Supplies of 35 countries, including several from Africa, showed that Africa had the lowest level of access to insulin for T1D patients.[103] Half of the respondents

reported that patients could only access insulin less than 50% of the time. While cost was the major barrier to access, unavailability in rural areas, lack of education, transport difficulties and storage issues were additional barriers. The Congo, DRC, Cote d'Ivoire, Madagascar and Togo reported that 50-70% of their patients who required insulin were unable to access insulin because it was too expensive. Mali and Uganda reported that 25-49% of their patients had this problem, while Nigeria and Senegal reported that only 1-24% of their patients encountered this barrier. Seychelles was the only African country in this survey that reported that all of their patients who needed insulin could obtain it on a consistent basis.[103]

This survey found the following prices (on average) for insulin in Africa: public sector = 10 (2.5 – 34) USD, private sector = 11.10 (2.5 – 36) USD, and NGO = 4.5 (2.5 – 20) USD, and insulin pens: public sector = 24 (6.40 – 60) USD, private sector = 60 13.60 – 80) USD, and NGO = 45 (30 – 60) USD. Diabetes supplies are also expensive as the median price ranges for 100 syringes and needles in Africa were: public sector = 20.50 (12.8 – 33.30) USD, privates sector = 32.90 (18.80 – 49.30) USD, and NGO = 20 (9 – 33.30) USD. Monitoring supplies were also pricey with the median price ranges for blood glucose meters the region being: public sector = 105 (53-125) USD, private = 103 (65 – 156.50) USD, and NGO = 82.50 (1 – 125) USD while strips alone were on average: public sector 49.50 (18 – 62.50) USD, private sector = 41.10 (30 – 102) USD, and NGO = 40 (39 – 40) USD. Countries were asked to rank the top four reasons for not testing in their country and the African countries responded that (1) cost of testing supplies, (2) lack of testing supplies, (3) lack of diabetes education, and (4) no patient interest were the major reasons for not testing.[103]

Each of these items represents a large portion of an average individual's yearly income and are therefore prohibitively priced. When they calculated the financial impact of diabetes care

in several selected countries (calculated the percentage of the GDP a person might spend a year on diabetes care items – assuming one 10 mL vial of insulin per month, 6 syringes per month, and one test strip per month) the results ranged from only 3% of the GDP in the Seychelles to 63% for the DRC.[103]

To allow countries to have their own means of assessing their barriers to insulin, the Rapid Assessment Protocol for Insulin Access (RAPIA) was developed. It is a series of questions that review the path of insulin from the moment it arrives in country until it reaches the patient.[104] It allows each country to identify barriers and gaps in infrastructure that prevent diabetic patients from receiving necessary care. It has been tested in three countries (Mozambique, Zambia an Mali) and has acted as a catalyst in bringing diabetes care to the attention of the local health authorities.[89]

Additional private company efforts have been made to make insulin more affordable. Novo Nordisk initiated an equity pricing initiative which offers insulin to the 50 poorest countries at prices that are less than 20% of the normal.[105] However, these services are limited as there are several African countries that are not included in this list, the information which Novo Nordisk provides to these countries is often lacking or confusing and this service is not offered to the private sector from which most patients receive their diabetes care.[92]

Efforts in individual countries are often supported by local teaching universities or through support from outside funders. One effort in Soweto, South Africa reduced their number of hyperglycemic emergency admissions rates and mortality by increasing education for their staff and patients, as well as developing formal treatment protocol.[106] In Ghana, a restructuring of their care system leading to nurse-led patient education sessions also resulted in lower rates of hospital admissions and mortality related to diabetes.[107] Significant decreases in HbA1c levels

were seen in rural KwaZulu-Natal in South Africa where they also used nurse-led educations systems in scattered primary health clinics.[108] Additional programs have seen similar results in Ethiopia[109] and Eritrea.[110] There are several newer programs such as the twinning initiative between the Diabetes UK and Mozambique Diabetes Association[111] and the new National Diabetes Program in Tanzania[112], which are also seeking to improve care for patients with diabetes in Africa.

In 2001, the LFAC program was established by the IDF in partnership with Australian Diabetes Council and HOPE*worldwide* to develop sustainable programs that provide access to care, education, and necessary diabetes supplies and therapy to children in developing countries. It is currently supporting over 4,000 children in 28 countries. LFAC works with the local authorities to build their capacity to address the diabetes situation in sustainable ways. There are several sites in Africa, including one in Kigali, Rwanda, which is operated by the Association Rwandaise des Diabetiques (ARD). In 2008, Eli Lilly and Company announced that it would donate more than 800,000 insulin vials to children in nine sub-Saharan African countries through the IDF's Life for a Child (LFAC) Program. The goal of this cooperation and donation is that by 2012, they will be able to provide life-saving insulin and supplies to up to 24,000 children.[113]

2.8 RWANDA

Rwanda is a country located in the Great Lakes Region of East Africa and has a population of roughly 11.05 million people living within 26,338 sq km (roughly the size of Maryland), making it the most densely populated country in Africa.[114] Since the 1994 genocide, Rwanda has made great progress both economically and socially under the direction of President Paul Kagame. However, 56.7% of Rwandans still live under the poverty line, with 37% living in extreme

poverty.[115] Due to the genocide and previous disease epidemics, there were 613,000 orphans living in Rwanda in 2001, and an estimated 101,000 children are living in child-headed households.[116] These conditions lead to quality health care being prohibitively expensive for these children and thus make diagnosis of a chronic disease, like diabetes, essentially a death sentence in many cases.

The operations of the LFAC program in Rwanda are overseen by Mr. Francois Gishoma. Mr. Gishoma has a first-hand understanding of the ever-continuous needs of diabetic patients, as he himself has the disease. The Rwandan LFAC program was initiated in 2004 with the enrollment of 25 children at the ARD. The LFAC program originally was designed to support children up until age 23, but in early 2009, the cutoff age was moved to 25. Since its conception the program has expanded in numbers and scope. The LFAC program is now active at the ARD and over 18 district hospitals countrywide. There has been a steady increase in the number of children participating, as 93 children were enrolled in 2007, 181 in 2008, and 301 by the end of 2009. It is believed that the increased number of participants is a reflection of an increase in awareness and the seeking of care rather than an actual increase in the incidence of the disease. However, due to the lack of studies of incidence and prevalence in this country, it is not possible to know whether any increase in incidence has occurred.

The University of Pittsburgh Graduate School of Public Health initiated a partnership with the ARD in 2007, and has since been very actively providing assistance and guidance to the program. Every summer since 2009 a Master of Public Health Student, under the guidance of Dr. Trevor Orchard, has traveled to Rwanda for a period of 6 weeks to assist with the annual assessment of the LFAC participants, a process essential to receiving supplies from the LFAC. Each year, data on: date of birth, date of diagnosis, number of injections a day, units of insulin a

day, type of insulin used, average visits to a doctor per year, height, weight, blood pressure, eye function, neuropathy, HbA1c, A/C ratio, number of hypoglycemic episodes, number of hospitalizations, and school attendance is collected for each participant.

Dr. Orchard is also the principal investigator of a new comparative effectiveness clinical trial based in this population. The grant is funded by the National Institute of Diabetes, Digestive, and Kidney Disease, and aims to establish a pilot study comparing a simplified diabetes management protocol based, initially, on a single daily basal insulin, to the current conventional management which involves combined regular and NPH insulin. The trial is currently in recruitment phase and will hopefully improve diabetes care for youth in the developing world and throughout the LFAC program.

2.9 SUMMARY AND SIGNIFICANCE

Each year, the worldwide incidence of type 1 diabetes rises by approximately 3%.[14,15] However, since there are geographic differences in the rates of this disease, it is important for Public Health officials to have an accurate estimate of the prevalence in their country. This way they will know the true magnitude of the burden for this disease. It is also important that each country has access to management methods that have been proven to work in populations similar to their own. These data are both vital and necessary to providing sufficient and correct care to patients. Unfortunately, these data are lacking or completely absent in most developing countries, which could benefit the most from such information.

The proposed study will work towards filling in several of these gaps for one specific developing country: Rwanda. Through our work we hope to 1) gather representative prevalence data from several districts across the country, allowing us to estimate countrywide prevalence

and look for within-country geographic variances. This data collection process will also enable the establishment of a youth onset diabetes registry 2) determine the short-term natural history of diabetes by following up all previously identified cases 3) record the effects of directed and monitored patient care provided by the ARD. All together the results may help direct future disease management, care, and resource allocation in Rwanda, but it is hoped the findings will be relevant to many countries in Africa and beyond.

3.0 SPECIFIC AIMS

The Rwandan LFAC program was initiated in 2004 with the enrollment of 25 children at the ARD, but has since expanded to supporting 522 children by July 2011. Data from these children will be used to examine the following specific aims:

Specific Aim 1: *To execute a 1-2 year follow up of the LFAC 2009-2010 cohort using HbA1c to evaluate the impact of regular HbA1c testing and organized, structured care on glycemic control. Follow up data of prevalence of complications and mortality will also be presented.*

Specific Aim 2: *To document and register eligible children and youth (age 25 and younger) with clinically diagnosed type 1 diabetes in six representative districts and Kigali City.*

Specific Aim 3: *To follow up the first 500 cases registered with the ARD from 2004 – 2011. Data on: utilization of the program (number and frequency of visits), losses to follow up, clinical characteristics, laboratory measures, complications (acute and chronic) and mortality will be presented.*

4.0 GLUCOSE CONTROL IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES IN RWANDA FOLLOWING PROGRESSION OF CARE

To be submitted for publication

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4.1 ABSTRACT

AIMS: To assess glycemic control concurrent with introduction of quarterly clinic visits with HbA1c testing, and increased patient and provider education with a 1-2 year follow up of the Rwanda Life For a Child (LFAC) 2009-2010 cohort. Additionally, patterns of HbA1c change, and complications were examined.

METHODS: Participants were members of the Rwanda LFAC program (aged $\leq$ 25 years) with first HbA1c measure between June 2009 and November 2010. Data were analyzed for the entire cohort and stratified by age (< 18 years, $\geq$ 18 years). Trajectory analysis was performed to identify group trends in HbA1c change.

RESULTS: Mean overall HbA1c decreased significantly from baseline (11.2±2.7%) to one- (10.2±2.6%) and two- (9.8±26%) year follow up visits. The prevalence of microalbuminuria (MA) did not significantly change (21.0%, 18.8%, and 19.6%), nor did nephropathy (4.7%, 7.8%, and 5.4%), or neuropathy (2.1%, 1.2%, and 0.0%). The prevalence of hypertension (31.8%, 44.9%, and 40.3%), however, were higher than expected and increased significantly. Five HbA1c control groups were identified by trajectory analysis, and those with the worst glucose control monitored their glucose significantly fewer times per week.

CONCLUSIONS: These data demonstrate that implementation of regular care, HbA1c testing, and increased education can result in significant improvements in glycemic control in youth and adolescent type 1 diabetes (T1D) patients in sub-Saharan Africa, but highlight the need for continued monitoring of complications.

4.2 INTRODUCTION

Diabetes is a non-communicable disease (NCD) of increasing global concern, especially for resource-limited developing countries. In sub-Saharan Africa, an estimated 18.7 million people will be affected by this disease by 2025.[2] Access to necessary insulin and management options are often limited in these areas. This may prevent patients from achieving adequate glycemic control that is necessary for the prevention/delay of disease sequelae.[60,89,117]

In order to address this problem, outside support has been necessary, as access to insulin is greatly limited.[92] One program providing such help is the International Diabetes Federation's Life For a Child (LFAC) program, which is managed in conjunction with the Australian Diabetes Council and HOPE *worldwide*. LFAC's mission is to support the provision of the best possible healthcare, given local circumstances, for children and youth with diabetes ($\leq$ 25 years) in developing countries. This is achieved by strengthening diabetes services through the provision of insulin, syringes, glucose monitoring supplies, HbA1c testing, diabetes education and expert advice and training. One program receiving assistance from LFAC is the Association Rwandaise des Diabetiques (ARD) in Kigali, Rwanda – the only specialized care provider for diabetic patients in Rwanda.

The Rwanda LFAC program at the ARD was initiated in 2004 with 25 children receiving support and annual clinic visits. The program has expanded since then, and as of the end of 2011, 634 children and young adults were enrolled. The ARD has also been aided by the University of Pittsburgh Graduate School of Public Health (GSPH), which sends a Masters of Public Health (MPH) Student each year to assist with the annual assessment of the youth.

We previously reported on the first 286 children and youth with type 1 diabetes (T1D) in the LFAC Rwanda program, who had their first HbA1c test between June 2009- November

2010.[118] The overall level of glucose control was very poor with a mean HbA1c of 11.1±2.8%, and 30.9% (n=88) having HbA1c above 14%. Complications were also already present in this population, despite the mean diabetes duration of only 3.4±3.1 years.

Since baseline, the care provided by the ARD has evolved, with the support of GSPH, through the implementation of quarterly clinic visits with HbA1c testing and microalbuminuria (MA) assessment as needed. Additionally, patient and provider education on daily diabetes management has increased. The primary objective of this report, therefore, is to assess the change in glucose control concurrent with this evolution of care with a 1-2 year follow up of the Rwanda LFAC 2009-2010 cohort. We will also examine patterns of HbA1c change, determine the characteristics of those developing complications, and those not returning for follow-up.

4.3 METHODS

This report is a quality improvement project of the LFAC Program in collaboration with the ARD and GSPH. The University of Pittsburgh's IRB has determined that this project is exempt from review under the "Existing Data" category.

4.3.1 Study Population

All participants in this evaluation were registered members of the Rwanda LFAC program who had their first HbA1c measure between June 2009 and November 2010.[118] To be enrolled in the program, participants must be citizens of Rwanda aged $\leq$ 25 years needing assistance with

obtaining insulin and diabetes supplies. Participants either sought out care from the ARD or were referred by their physicians or healthcare providers.

Diabetes care for the LFAC participants in Rwanda has evolved over the last several years as outlined in table 6. This single-nurse led program started in 2004, but regular HbA1c testing was not available until 2009 and only annual visits were required until 2010. Since then, the program has expanded in size and scope through providing support to numerous district hospitals and development and execution of patient and care provider education sessions. While attempts have been made to improve provider care at hospitals, due to staff rotation and relative unawareness of diabetes in youths, the quality of care still remains a problem.

4.3.2 Data Collection

Baseline data were collected from June 2009 – through November 2010. Baseline and follow up data were collected using the LFAC forms and protocol (previously described[118]) either at the ARD or at several district hospitals supported by the program. Follow up data were collected from baseline through April 30, 2012 by the ARD staff and University of Pittsburgh students. This timing of follow up meant that 79 subjects were not yet eligible for a two- year follow up visit. All assisting University of Pittsburgh students and ARD clinical staff were trained by authors TO and DE.

No data were collected for research purposes and all data reported are routinely recorded for clinical care purposes.

Laboratory Data

Blood and urine samples were processed on the Siemens DCA Vantage™ by the MPH students or ARD staff. HbA1c and Albumin/Creatinine (A/C) ratio results were reported to the nearest tenth percent. The maximum HbA1c value for this machine is ">14 %," so for data analysis

purposes these results were reported as "14.1." Regular quality control testing resulted in a coefficient of variation for the DCA of 2.1% to 3.8% during data collection.

Anthropometric and Blood Pressure Percentiles for Youth

Height and weight were measured with a stadiometer and floor scale, respectively. Height was recorded to the nearest 0.1 cm and weight to the nearest 0.5 Kg. Blood pressure (BP) was assessed with a manual cuff for a portion of 2009 and then by an automatic BP machine (Omron Healthcare, Inc.) and cuff for the duration of follow-up. Cross-over studies showed no significant differences between methods, and post hoc analysis showed no trends in data due to this change. For those under age 18 years of age, height for age,[119] systolic and diastolic BP for height percentile and age,[120] and BMI for age[121] percentiles and z-scores were calculated. It should be noted that the percentiles and z-scores are based on US standards as no appropriate Rwanda data are available. Short stature was defined as those under the 5th percentile.[119] Those under the 5th percentile for BMI were considered to be underweight, those from the 5th to 84th were normal weight, 85th to 94th were overweight, and those over the 95th percentile were obese.[121] For systolic and diastolic blood pressure, those over the 95th percentile were considered hypertensive.[120]

For those over 18 years of age, a BMI under 18.5 was scored as underweight, 18.5-<25 normal weight, 25-30 overweight, and over BMI of 30 obese.[122] Hypertension was defined as a systolic BP ≥130 mmHg or diastolic BP ≥80 mmHg or a history of BP medication. The number of those using BP medication, however, is low due to high costs.

4.3.3 Patient and Provider Education

Initially (2008-2010), education for patients focused mostly on proper injection of insulin, how to adjust insulin doses appropriately based on food availability and glucose monitoring results, when available, and recognizing hypoglycemia and the appropriate actions to take. Additional education materials and information were later (2011) introduced on: relevance of HbA1c, what to do when blood sugar levels are very low (hypoglycemia), when to call the clinic, possible complications from diabetes, proper nutrition, how to account for exercise, and what to do when sick with an infection. Education for care providers focused mainly on the different insulins available, how to properly prescribe and adjust insulin doses, and how to handle hypo- and hyper-glycemia.

4.3.4 Complication Assessment

Neuropathy

Neuropathy was defined as failure to feel a 10g monofilament (<7 of 10 correct responses) on the dorsum of the great toe and/or failure to feel vibration from a 120Hz tuning fork on the dorsum of the great toe for longer than 10 seconds.[123]

Microalbuminuria

Microalbuminuria (MA) was defined as an albumin/creatinine (A/C) ratio of 30-299 mg/g in a spot urine sample, and overt nephropathy as an A/C ratio $\geq$ 300 mg/g.

4.3.5 Data Analysis

Descriptive statistics including mean, standard deviation and frequencies were calculated for all variables. Two-sample and paired t-tests, chi squared test and Fishers Exact tests were used as appropriate for comparisons. Spearman correlation coefficients were used to assess the association between HbA1c and other continuous variables of interest at each visit. When examining changes in anthropometric data over time, only subjects who were $\geq$18 years for the entirety of follow up or <18 years for the entirety of follow up were included (thus excluding n=9 from baseline to visit-1(V1) and n=20 for baseline to visit-2 (V2)) to account for the few that were <18 years at baseline but were $\geq$ 18 years at either V1 or V2. Analysis of variance was used to assess differences in BP by HbA1c control group and Tukey's HSD was used for post-hoc analyses.

Logistic regression modeling was used to identify factors that predict MA. Univariate associations were first examined to identify contributors and those with significance of $p \leq 0.2$ were then considered for inclusion in the final model. Backwards stepwise regression was then completed using a significance of $p < 0.05$ for inclusion. Age was retained as a potential confounder.

Trajectory analysis was performed using the PROC TRAJ macro (found at http://www.andrew.cmu.edu/user/bjones/) to determine if there were distinctive HbA1c trajectory profiles within the overall population using group-based semiparametric mixture modeling. This macro uses longitudinally collected data to define trajectories and then categorize participants into those groups based on a posterior probability.[124] We used data that were collected at baseline and at 3-month intervals up to 24 months. Given the censored distribution of

our data, we used a censored normal model. To determine the number of trajectories, we used the Bayesian information criterion (BIC) log Bayes factor approximation:

$$2\log_e(B_{10}) \cong 2(\Delta BIC)$$

where ΔBIC is the BIC of the more complex model less the BIC of the simpler model.[124] After participants were classified into trajectory groups, we examined differences in other factors using the PROC Mixed procedure in SAS.

The analysis for this paper was generated using SAS/STAT software, Version 9.3 of the SAS System for Windows, copyright © 2011 SAS Institute Inc.

4.4 RESULTS

A total of 214 children and youth (of 286) had an HbA1c measurement one year (V1) (11.7±2.3 months) after their baseline (BL) measurement and 144 had a follow up measurement two years (V2) (23.0±3.5 months) after baseline. 125 participants attended both V1 and V2 and therefore comprise a full compliance (FC) sub-group. Age specific measurements (<18 years/≥18 years) can be seen in supplemental tables 1 and 2 (Appendix A).

At baseline mean age, diabetes duration and glucose monitoring frequency were 18.6±4.5 years, 3.4±3.1 years and 1.1±3.4 times per week, respectively (table 7). A high percent (48.2%) of those <18 years had short stature and 16.1% were underweight (table 7). Complications were already present in this cohort with MA (21.0%) and hypertension (31.8%) being the two most common (table 7).

There were no significant differences in baseline characteristics for those who attended V1 and those who did not, although, those who attended V1 were somewhat younger at baseline

(p=0.07) and took more insulin per kg (p=0.07) (table 7). Height at baseline was the only characteristic that was borderline different at V1 for those <18 years (p=0.07) (table 7). Those who attended V2, however, were significantly younger at baseline (17.5±4.7 years vs 19.9±4.3 years) and had borderline lower systolic BP (p=0.08) and more frequently monitored their glucose levels (p=0.06) than those who were eligible for V2 but did not attend (table 7). At baseline, for those <18 years, HbA1c was negatively correlated with systolic BP z-score (r=-0.2, p=0.03) and for those ≥18 years it was negatively correlated with systolic BP (r=-0.2, p=0.007) and positively correlated with units of insulin/kg (r=0.2, p=0.002).

At V1 participants monitored their glucose more frequently (2.6±4.7 times per week vs 1.0±3.2 times per week; at BL 3.3% monitored 2+ times per week, at V1 = 8.0%) and had higher systolic (118±16 mmHg vs 112±14 mmHg) and diastolic (77±13 mmHg vs 72±11 mmHg) BP than at baseline (table 8). Similar patterns were seen for the FC sub-group (data not shown). For those <18 years, systolic and diastolic BP z-scores were higher at V1 than baseline as were rates of hypertension (table 8). For those ≥18 years, mean systolic (115±14 mmHg at BL vs 122±15 mmHg at V1) and diastolic (74±11 mmHg at BL vs 79±13 mmHg at V1) BP significantly increased (table 8). At V1 HbA1c was negatively correlated with monitoring frequency (r= -0.4, p=0.004 <18 years; r=-0.3, p<0.0001 ≥18 years) and height z-score (r=-0.3, p=0.02).

At V2 mean glucose monitoring frequency (1.7±4.4 at BL, 2.5±4.4 at V1 and 6.6±6.9 at V2; at BL 6.3% monitored 2+ times per week, at V2=33.1%) per week was significantly higher than both previous visits. For those <18 years, mean systolic and diastolic BP z-scores were significantly higher at V2 than baseline. For those ≥18 years mean systolic (115±16 mmHg at BL vs 122±21 mmHg at V2) and diastolic (75±11 mmHg at BL vs 80±14 mmHg at V2) BP were higher than baseline but not V1 (table 3). At V2 HbA1c was negatively correlated with BMI z-

score (r=-0.3, p=0.03) for those <18 years, and with glucose monitoring frequency (r=-0.3, p=0.04) for those ≥18 years.

Figure 2A shows a significant decrease in mean HbA1c for the entire cohort from 11.2±2.7% at baseline to 10.2±2.6% (*P* <0.0001) at V1, and to 9.8±2.3% at V2 (*P* <0.0001 from BL, *P* <0.0001 from V1) (table 8). Very similar changes (*P* <0.0001) were seen in the FC sub-group (figure 2B). At V1, 56.1% (n=120) saw a 0.5% improvement or greater in HbA1c, and 66.7% (n=96) saw similar improvements at V2. In the overall cohort, at baseline, only 15.7% of participants had HbA1c <8%, but this increased to 23.6% at V2 (p=0.04). The most striking change was the decrease in the percentage of participants with HbA1c >14% from 30.8% at baseline to 12.2% at V1 (p<0.0001), and to 9.0% at V2 (p<0.0001 from BL, not significant from V1, Figure 2A, table 8). Similar patterns were seen for those in the FC sub-group (figure 2B). At baseline, 10.8% of participants met the ADA glucose control goals for their age, 13.1% met the goals at V1, and 12.5% at V2.

4.4.1 Trajectory Analysis

In order to identify factors that were associated with improved glucose control we used trajectory analysis to identify different groups of participants based on their HbA1c patterns over time. Of the 201 participants with sufficient data, five distinct groups were identified (Figure 3): Group 1 (N=16, 8.0%) – started low and stayed low, Group 2 (N=17, 8.4%) – started low then increased, Group 3 (N=54, 26.9%)– started intermediate then declined, Group 4 (N=64, 31.8%)– started high then declined, Group 5 (N=50, 24.9%)– started high and stayed high. There were no significant differences in age, age at diagnosis, or diabetes duration among the groups.

Repeated measures analysis was used to identify significant differences in clinical measures or behaviors by group. Only glucose monitoring per week was significant. Those in Group 5 (high-high) monitored their glucose on average fewer times per week than all other groups (Group 1 to 5 p=0.006; Group 2 to 5 p=0.01; Group 3 to 5 p=0.002, Group 4 to 5 p=0.04), and those who were in Group 3 (intermediate-decline) monitored on average significantly more frequently than those in Group 4 (high-decline) (p=0.002).

4.4.2 Complications

The annual prevalence of MA remained fairly constant (21.0% at BL, 18.8% at V1, and 19.6% at V2), as did nephropathy (4.7%, 7.8%, and 5.4%) and neuropathy (2.1%, 1.2%, and 0.0%) (tables 6 and 8). Hypertension, rates, however, increased significantly over time (31.8% at BL, 44.9% at V1, and 40.3% at V2).

In the FC sub-cohort, eight cases of MA were noted at V1, comprising 4 new cases; 1 who had improved from nephropathy at baseline, and three cases with continued MA from baseline. Ten cases of MA were noted at V2, comprising 7 new cases and 3 cases with continuing MA. The tentative estimate of the annual incidence of MA was therefore 16.6% (95% CI 7.0-42%) and the annual regression rate was 23.5%. One new case of nephropathy was identified at V1, which had progressed from MA at baseline. At V2, there was 1 additional case that previously had MA at baseline. The annual incidence of nephropathy was, therefore, 4.9% (95% CI 0.8-17%). The total N for those with complications was too small to design any meaningful models to identify predictors.

We stratified weight, systolic BP, and diastolic BP by the HbA1c control groups in the FC subgroup to see if HbA1c control impacted hypertension (table 9). While there were no overall significant differences, BP increased the most for Group 2 (low-increased) and the least for Group 1 (low-low), while BP for Group 3 (intermediate-low) remained fairly constant. Although BP also increased for Group 4 (high-declined), it was likely as a result of improved health, as previously described for this cohort,[118] since weight also increased as HbA1c decreased. Our total N was too small to detect any significant correlations between HbA1c control groups and BP, but BP increased with worsened HbA1c control (Group 2), and lessened with improved HbA1c control (Group 3). Even with improvements in control, Groups 3 and 4 still had higher BP than Group 1 which had consistently low HbA1c. Rates of hypertension also decreased with alterations in the definition of hypertension, with the biggest change due to adjustments to diastolic BP requirements (table 8).

Rates of MA, neuropathy, and nephropathy did not differ significantly by trajectory group; however, the sample size and event N were too small for analysis.

4.5 DISCUSSION

In this follow up of children and youth (≤25 years) with diabetes in Rwanda after the introduction of more systematic care, regular HbA1c testing, and education, we saw significant increases in glucose monitoring and blood pressure, and significant decreases in overall mean HbA1c (BL=11.2±2.7%, V1=10.2±2.6%, V2=9.8±2.6%) (tables 7 and 8). While the percentage of those meeting ADA glucose control goals for their age increased, the rates in Rwanda are still significantly lower than those seen in the US (under 6 years=64%%, 6-<13years =43%, 13-<20 years =21%).[125] We did not find any baseline predictors of V1 attendance, but those who

attended V2 were significantly younger at baseline than those who did not attend V2. Except for MA and hypertension, prevalence rates of complications were low, and did not change significantly over the follow up period.

We also identified five distinct HbA1c control groups through trajectory analysis, and these groups differed by frequency of glucose monitoring per week, with those with the worst control (Group 5; high-high) measuring significantly fewer times per week than all other groups. As HbA1c decreased with each follow-up visit, it was negatively correlated with monitoring frequency. These findings suggest that higher emphasis should be placed on more frequent glucose monitoring to improve glycemic control.

In support of our results, similar studies in sub-Saharan Africa report using education and HbA1c measurements to improve glucose control. These studies of older diabetes patients - one in Eritrea (n=350, mean age 50.5±15.5 years and duration 8.6 years),[110] and another in Kwazulu Natal, South Africa (n=284 with 197 completing; mean age 56±11 years and mean duration 7±6 years)[108] showed that improving the availability of HbA1c measurements and implementation of educational programs for physicians and diabetes educators, led to significant decreases in HbA1c (from 9.2±2.5% to 8.7±2.3% in Eritrea with mean follow up of 153 days; and from 11.6±4.5% at baseline to 8.7±2.3% by 6 months and 7.7±2.0% at 18 months in South Africa). A further study from Kenya also showed improvements in glucose control through increases in glucose monitoring and regular contact with community diabetes care workers. At baseline, 43 participants had a mean HbA1c of 13.2% (95% CI 12.8-13.5), but this had fallen to 10.5% (95% CI 9.8-11.1) by 3-6 months.[126] Though there were no demographic data presented for comparison to our cohort, this study in Kenya highlights the importance of not just HbA1c knowledge, but also use of regular glucose monitoring to adjust insulin doses. In our population

we saw a significant negative correlation between glucose monitoring and HbA1c at V1 and V2, suggesting that improvements in glucose monitoring frequency were associated with improved glucose control. Studies from the developed world, for example Germany and Austria, also support these findings, showing that glucose monitoring frequency is associated with 0.20%[127] and 0.26%[128] reductions in HbA1c.

Several of these previous studies included both type 1 and 2 diabetes patients, thus limiting any direct comparisons. Only 59% in Eritrea were taking insulin and even fewer were in South Africa (4%).[108,110] In the current study we believe the vast majority of our patients are type 1, based on their age at onset, lack of obesity, and insulin dependency. However, formal antibody testing and c-peptide testing were not available in our, or the other studies. However, the current study would thus appear to be the first report of improved diabetes control with regular HbA1c testing and education in a predominantly T1D population in sub-Saharan Africa.

The incidence of MA and nephropathy were estimated to be 16.6% and 3.3%, respectively. However, with the high rates of missing A/C data, patterns are uncertain. The incidence rates in our population appear quite high, especially in a young population with such short diabetes duration, and are almost 8x as high as those seen in Denmark (MA=1.9%)[129] and higher than in Australia (MA=4.6/1,000 person years)[130]; even with a shorter duration (~ 4 years for Rwanda vs 12.2 for Denmark and 6.7 years for Australia). However, HbA1c in Rwanda (11.2% vs 9.7%) was higher and was likely the driving factor for the higher rates.[60,131,132] The prevalence of MA in Rwanda, however, was slightly lower than reports from a Pittsburgh cohort aged 6-21 years with 5 years of diabetes duration (similarly aged Rwanda cohort MA=15.1%; Pittsburgh=21.0%),[133] suggesting that there may not be any actual increased prevalence of MA in Rwanda.

This population was lean and short based on US standards. Rates of obesity and overweight in those <18 years were very low (0.0-3.2% obese; 3.9%-7.2% overweight) in comparison to US youth with T1D in the SEARCH study (13.0% obese; 21.2% overweight).[134] Although the low rates are likely due to insulin deficiency and uncontrolled diabetes, many of these children and youth were born during or just after the Rwandan genocide, which could also have contributed to their small stature.

The mean values for SBP and DBP (112±14 and 72±11 mmHg) at baseline were similar to those for African American (AfAm) youth with T1D (112±11 and 73±11), but the rates of hypertension at baseline were significantly higher in Rwanda (AfAm=9.8%, Rwanda 30.8%).[11] An additional study of T1D in youth in the US (aged 6-21 years, 5 years duration) also showed significantly lower rates of hypertension than seen in Rwanda (% sbp $\geq$120 mmHg Pittsburgh USA =11.9% Rwanda=28.6%; % dbp $\geq$80 mmHg Pittsburgh=10.2%, Rwanda=42.8%).[133] The increased rate of hypertension was likely driven by the high number of Rwandans with a diastolic BP of exactly 80 mmHg (n=30; 20%). When hypertension was defined as 130/85 mmHg, the percent of hypertensive Rwandans (16.4%) was much more similar to that in the US (table 8). We saw sizeable drops in hypertension prevalence at each visit when the definition of hypertension was increased by 5 mmHg for diastolic BP (130/85), though the same changes were not seen for a 10 mmHg increase in systolic BP (140/80). This suggests that most of the excess hypertension in this population is due to the high percent of Rwandans with diastolic BP around 80 mmHg.

It is likely that poor glucose control was the driving force for the increased rates, as evidenced by the increased BP for those whose control worsened (Group 2) and the decrease for those with improved care (Group 3). It is important to note that even with improved control, BP

remained higher than for those with constant tight control. This implies that there was a residual effect of poor control, even after improvements. Previous work from a US cohort of youth with T1D (mean age 12.5±4.4 years, mean duration 4.5±3.3 years) showed a significant positive correlation between HbA1c and diastolic BP.[135] However, due to the small N, as well as the potential for hypovolemia in those with very poor glycemic control we saw no such significant correlations between HbA1c and diastolic BP in our population.

It is possible that other factors also contributed to the excess hypertension in this population. Previous studies found that the prevalence of hypertension in those under age 45 years was higher in sub-Saharan Africa (SSA) than the US and the UK (SSA=10.7%, UK=5.6%, US=8.2%).[136] Diet may be a factor, as salt is often used in food preparation and preservation in SSA.[136] However, no dietary records were kept for our population, so we were unable to determine its impact. Unfortunately very few participants were taking BP medication due to prohibitive prices. This represents a considerable constraint on furthering care for those in need, and additional funds are needed to address this issue.

The major strength of this report is that it is the first such study showing that improvements in glucose control can be obtained in children and adolescents with T1D in sub-Saharan Africa. We have also been able to provide preliminary estimates of the incidence and prevalence of MA and nephropathy in this population.

While 74.8% of our original cohort attended V1 and 84.7% of those eligible were seen at V2, these rates are lower than desired, and give rise to concern as to the current vital status of those who did not attend. Though, several of the participants (N=10 at V1, N=16 at V2) would have been over age 25 at both visits, follow up of the remaining missing participants is a major focus of our current plans.

Complication assessment is limited, as only a small proportion have had their A/C measured (41.2% at baseline, 29.9% at one-year, and 38.9% at two-years), which is a reflection of lack of supplies and examination logistic issues. Assessment of neuropathy was also limited because it was only recorded on the annual LFAC form and not the quarterly form. Additionally, we were unable to assess retinopathy at this time, though we are currently working to address this for future care. Some clinic data were self-reported (monitoring frequency and units of insulin taken per day), so there is no way of monitoring compliance or the accuracy of these reports.

Though this cohort is representative of the LFAC program in Rwanda, it is possible that it does not reflect the true diabetes population. We believe, that due to poverty and lack of access to insulin, almost all cases are referred to the LFAC program for care and supplies, however, it is likely that we are missing undiagnosed cases as well as those who died before diagnosis. This would mean our cohort likely represents more of a survivor cohort.

In summary, our data from the 1-2 year follow-up of the 2009-2010 LFAC cohort demonstrate that implementation of regular HbA1c testing, provision of more regular care, and increased education may result in significant improvements in glycemic control in young ($\leq$25 years) T1D patients in sub-Saharan Africa. Trajectory analysis allowed us to identify sub-groups within our population that follow different control patterns and we identified glucose monitoring frequency as a potential specific area of intervention for improving glycemic control. In the future, use of this statistical method could result in more tailored management plans specific to each control group. While we have reported improvements, it is clear that there is still a great need for further increases in glucose control in Rwandan youth and adolescents with T1D, as

there are still several participants in this cohort with HbA1c >14%, and we saw a high prevalence of hypertension and early onset of complications.

4.6 TABLES

Table 6. Evolution of the LFAC program in Rwanda.

Year	Status
2004-2007	- Initiation of insulin availability - No organized clinical records or management protocol
2008	- Files organized for patient based follow-up - One-page LFAC form adopted - First University of Pittsburgh visit
2009*	- First MPH student visit - Addition of HbA1c and A/C ratio testing - Plan developed for quarterly follow-up - Provider and patient education sessions - Addition of several district hospitals
2010*	- Quarterly follow-up implemented - Additional training/mentoring for ARD staff - Development of additional education for LFAC participants - Increase in availability of testing supplies (intermittent since) - Expansion of number and frequency of district hospital visits
2011	- Further development of education materials - Further increase in number of hospitals - Increased frequency of education sessions by ARD staff
2012	- Program now covers 23 other hospitals across the country

* Baseline HbA1c measures were collected during these years

Table 7. Baseline characteristics of the 2009-2010 LFAC cohort overall, stratified by attendance at V1 (one-year) and V2 (two- year) visits.

	Overall	Attendance at V1		Attendance at V2	
		Yes	No	Yes	No[&]
N	286	214	72	144	70
Age (years)	18.6±4.5	18.3±4.4 ∓	19.4±4.7	17.5±4.7*	19.9±4.3
Male %(n)	46.5 (133)	44.9 (96)	51.4 (37)	35.4 (51)*	67.1 (47)
Diagnosis Age (years)	15.1±4.8	15.0±4.7	15.7±5.4	14.2±4.7*	15.8±5.3
Seen in 2009 %(n)	46.2 (132)	44.9 (96)	50.0 (36)	69.4 (100)*	45.7 (32)
Duration (years)	3.4±3.1	3.3±2.9	3.5±3.8	3.3±2.8	4.0±3.4
HbA1c (%)	11.2±2.7	11.3±2.7	11.0±2.6	11.4±2.5	11.2±2.6
HbA1c >14% %(n)	30.8 (88)	32.7 (70)	25.0 (18)	30.6 (44)	27.1 (19)
HbA1c <8% %(n)	15.7 (45)	16.4 (35)	13.9 (10)	11.1 (16)	18.6 (13)
Glucose Monitor / wk	1.1±3.4	1.0±3.2	1.4±4.2	1.7±4.4∓	0.66±2.1
Insulin units/kg	0.73±0.36	0.75±0.39 ∓	0.66±0.28	0.75±0.41	0.74±0.36
Height (cm)	154.2±14.7	153.6±14.6	155.8±15.1	151.6±14.5	156.9±17.3
Height Z-score[$]	-1.6±1.8	-1.8±1.8∓	-1.0±1.7	-1.7±1.8	-1.3±1.7
Short Stature %(n)[$]	48.2 (42)	52.3 (34)	36.4 (8)	46.2 (24)	42.9 (6)
Weight (kg)	48.1±12.7	47.6±13.0	49.3±11.9	46.7±14.0	50.5±12.2
BMI (kg/m^2)	20.2±4.0	20.1±3.9	20.2±4.3	20.2±4.1	20.5±4.8
Underweight %(n)	18.6 (53)	19.6 (42)	15.5 (11)	16.7 (24)	21.4 (15)
Healthy Weight %(n)	69.5 (198)	66.8 (143)	77.5 (55)	66.0 (95)	34.0 (49)
Overweight %(n)	5.0 (14)	5.1 (11)	4.2 (3)	6.9 (10)	1.4 (2)
Obese %(n)	2.1 (6)	2.3 (5)	1.4 (1)	2.8 (4)	1.4 (2)
BMI Z-score[$]	-0.7±1.4	-0.7±1.4	-0.7±1.1	-0.6±1.6	-0.6±0.8
Systolic BP (mmHg)	112±15	112±14	114±18	111±16∓	115±15
Systolic BP Z-score[$]	-0.1±1.0	-0.04±1.1	-0.4±0.7	-0.2±1.0	-0.1±0.8
Diastolic BP (mmHg)	72±11	72±11.0	72.7±11	72±11	74±10
Diastolic BP Z-score[$]	0.5±0.7	0.5±0.7	0.4±0.6	0.5±0.7	0.4±0.6
Hypertension %(n)[¥]	31.8 (91)	30.8 (66)	34.7 (25)	28.4 (41)	38.6 (27)
Microalbuminuria %(n)	21.0 (31)[a]	20.5 (23)[c]	21.6 (8)[e]	20.4 (21)[g]	21.2 (7)[i]
Nephropathy %(n)	4.7 (7)[a]	6.2 (7)[c]	0.0 (0)[e]	3.9 (4)[g]	3.0 (1)[i]
Neuropathy %(n)	2.1 (5)[b]	2.3 (4)[d]	1.6 (1)[f]	1.8 (2)[h]	5.1 (3)[j]

[&]Includes only those who were eligible for a two-year follow –up
[$]Indicates variable calculated for participants <18 years only
[¥]Rates were calculated by adding those who were <18 years and $\geq 95^{th}$ percentile with those who were ≥18 years and met the definition of hypertension based on BP

* Indicates significance at $\alpha < 0.05$
∓ Indicates borderline significance at $\alpha < 0.1$

a=118 tested; b=180 tested; c=112 tested; d=174 tested; e=37 tested; f=62 tested, g=103 tested, h=5 tested, I=33 tested, j=59 tested

Table 8. Clinical characteristics of one (V1) and two (V2) year follow up visits as compared to baseline and one-year data.

	V1		V2		
	Baseline	V1	Baseline	V1	V2
N	214	214	144	126	144
Male % (n)	44.9 (96)	44.9 (96)	35.4 (51)	36.5 (46)	35.4 (51)
Overall HbA1c (%)	11.3±2.7	10.2±2.6*	11.4±2.5	10.5±2.7	9.8±2.3$^{\lozenge}$*
HbA1c >14% %(n)	32.7 (70)	12.2 (26)	30.6 (44)	12.7 (16)*	9.0 (13)
HbA1c <8% %(n)	16.4 (35)	24.8 (53)	11.1 (16)	20.6 (26)*	23.6 (34)
Glucose Monitor / wk	1.0±3.2	2.6±4.7*	1.7±4.4	2.5±4.4	6.6±6.9$^{\lozenge}$*
Insulin units/kg	0.75±0.39	0.72±0.31	0.75±0.41	0.72±0.29	0.76±0.34
Height (cm)	153.6±14.6	155.7±14.4	151.6±14.5	154.5±15.2	154.4±14.3
Height Z-score$^{\$}$	-1.8±1.9	-1.8±1.9	-1.3±1.6	-1.8±1.8	-1.4±2.0
Short Stature %(n)$^{\$}$	55.4 (31)	52.5 (31)	39.4 (13)	40.7 (11)	37.8 (14)
Weight (kg)	47.6±13.0	49.8±12.3	46.7±14.0	49.6±12.6	49.9±12.4
BMI (kg/m^2)	20.1±3.9	20.2±3.1	20.2±4.1	20.4±3.2	20.6±3.3
Underweight %(n)	19.5 (40)	18.8 (38)	15.3 (19)	13.9 (15)	14.5 (18)
Healthy Weight %(n)	66.8 (137)	70.7 (145)	66.9 (83)	72.2 (78)	75.0 (93)
Overweight %(n)	4.9 (10)	6.8 (14)	6.4 (8)	7.4 (8)	8.9 (11)
Obese %(n)	2.4 (5)	0.5 (1)	2.4 (3)	0.9 (1)	0.0 (0)
BMI Z-score $^{\$}$	-0.7±1.4	-0.6±1.4	-0.4±1.4	-0.4±1.6	-0.4±1.1
Systolic BP (mmHg)	112±14	118±16*	111±16	117±15*	118±19$^{\lozenge}$
Systolic BP Z-score$^{\$}$	-0.07±1.0	0.3±1.3*	-0.3±0.9	0.7±1.3*	0.6±1.2$^{\lozenge}$
Diastolic BP (mmHg)	72±11	77±13*	72±11	76±13*	80±19$^{\lozenge}$*
Diastolic BP Z-score$^{\$}$	0.4±0.7	0.8±1.0*	0.5±0.7	0.8±1.0	1.4±1.0$^{\lozenge}$*
Hypertension (130/80) %(n) $^{¥}$	30.8 (66)	44.9 (96)*	27.8 (40)	38.8 (49)	40.3 (58) $^{\lozenge}$
Hypertension (130/85) %(n) $^{¥}$	16.4 (35)	34.6 (74)*	15.3 (22)	28.6 (36)*	31.3 (45) $^{\lozenge}$
Hypertension (130/90) %(n) $^{¥}$	15.4 (33)	28.5 (61)*	13.9(20)	23.0 (29)	25.7 (37) $^{\lozenge}$
Hypertension (140/80) %(n) $^{¥}$	29.4(63)	41.6 (89)*	27.8 (40)	35.7 (47)	39.6 (57) $^{\lozenge}$
Hypertension (140/90) %(n) $^{¥}$	10.7(23)	21.0 (45)*	10.4 (15)	14.3 (18)	25.0 (36) $^{\lozenge}$*
Microalbuminuria %(n)	20.5 (23)^{a}	18.8 (12)^{c}	20.4 (21)^{e}	18.8 (8)^{g}	19.6 (11)^{k}
Nephropathy %(n)	6.2 (7)^{a}	7.8 (5)^{c}	3.9 (4)^{e}	4.6 (2)^{g}	5.4 (3)^{k}
Neuropathy %(n)	2.3 (4)^{b}	1.2 (1)^{d}	1.8 (2)^{f}	1.4 (1)^{h}	0.0 (0)^{m}

* Indicates significance at $\alpha = 0.05$ to year before

$^{\lozenge}$ Indicates significance at $\alpha = 0.05$ to two -years before

a – 112 tested; b – 174 tested; c – 64 tested; d- 85 tested; e -103 tested; f -112 tested; g -44 tested; h -69 tested; k -56 tested; m- 5 tested.

$^{\$}$Indicates variable calculated for participants <18 years only

$^{¥}$Rates were calculated by adding those who were <18 years and $\geq$95th percentile with those who were $\geq$18 years and met the definition of hypertension based on BP

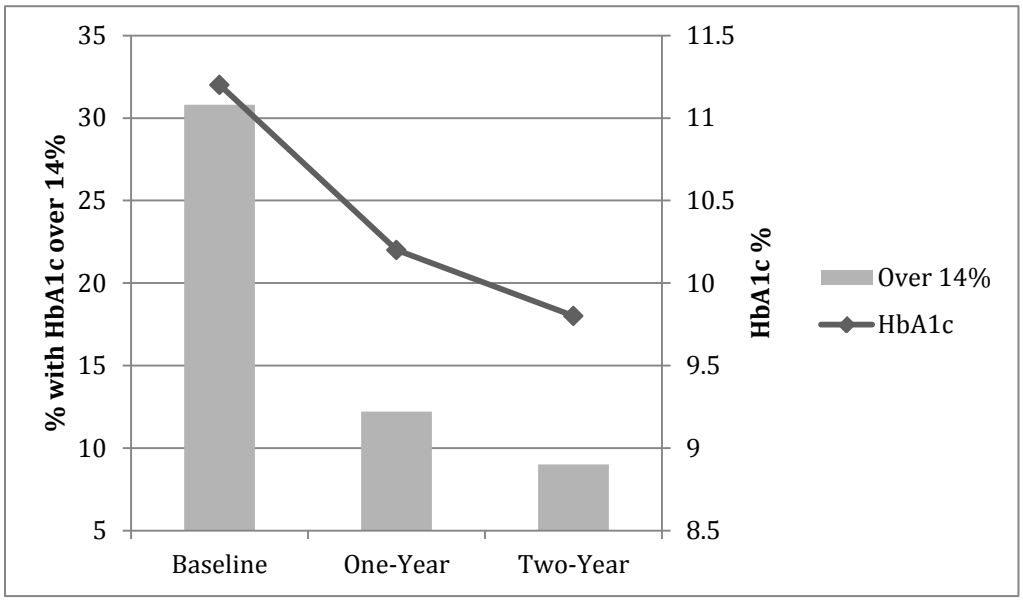
Table 9. Weight, BP, and HbA1c stratified by HbA1c control group for those >18 years who had full compliance.

	Group 1	Group 2	Group 3	Group 4	Group 5
	Low-Low	Low-Increased	Intermediate-Decline	High-Decline	High-High
N	7	6	23	23	17
Age at Baseline	20.4±1.8	20.2±1.5	20.4±1.6	20.8±1.5	19.6±2.0
Baseline systolic BP (mmHg)	117±17	107±15	120±10	111±16	117±16
Change BL-V1	6.7	24.0	0.2	6.3	4.6
Change BL-V2	-1.43	18.17	1.04	11.74	8.06
Baseline diastolic BP (mmHg)	79±13	70±9	78±10	72±11	74±15
Change BL-V1	-3.9	19.5$	1.4◊	3.4	3.2
Change BL-V2	-2.3	9.8	-0.1	10.2	7.8
Baseline weight (kg)	52.6±8.5	51.8±8.9	53.0±7.3	50.9±10.5	53.2±12.0
Change BL-V1	0.6	5.2	0.6	3.6	0.1
Change BL-V2	0.3	2.9	-0.2	2.7	2.9
HbA1c (%)	6.5±1.1	8.6±1.1	10.7±1.6	12.9±1.3	13.5±1.0
Change BL-V1	-0.3	0.6	-2.1	-2.4	0.1
Change BL-V2	-0.2	1.2	-2.6	-3.2	-2.0

*Indicates significantly different than Group 1
◊Indicates significantly different than Group 2
$Indicates significantly different than Group 3
+ Indicates significantly different than Group 4
¥ Indicates significantly different than Group 5

4.7 FIGURES

A



B

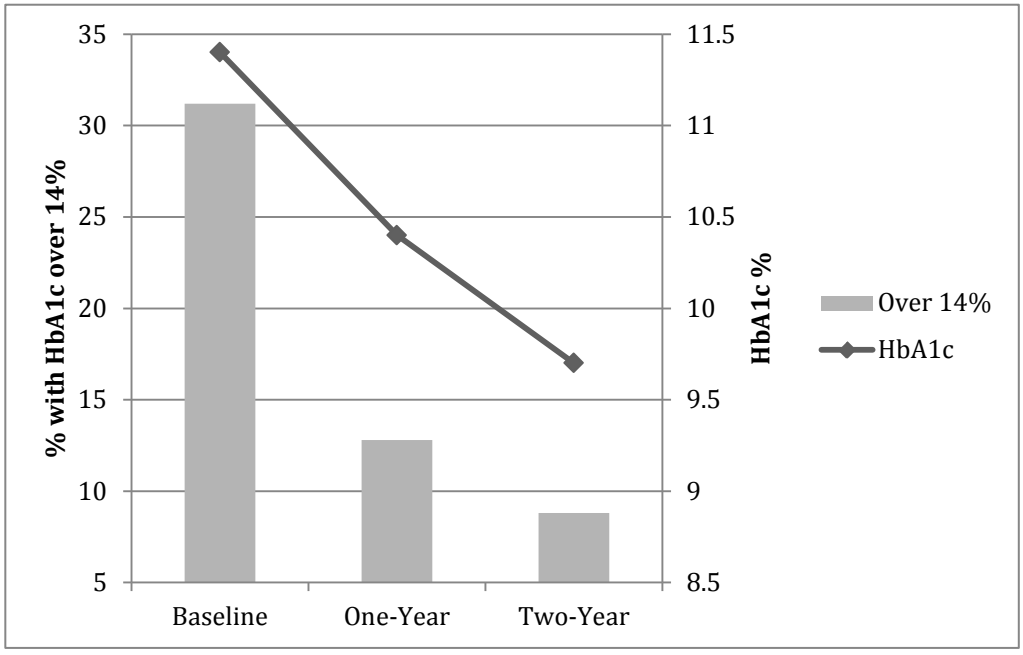


Figure 2. Mean HbA1c for A) overall cohort (n=286) and B) those who had full compliance (n=125), and % of population at each time with HbA1c over 14%

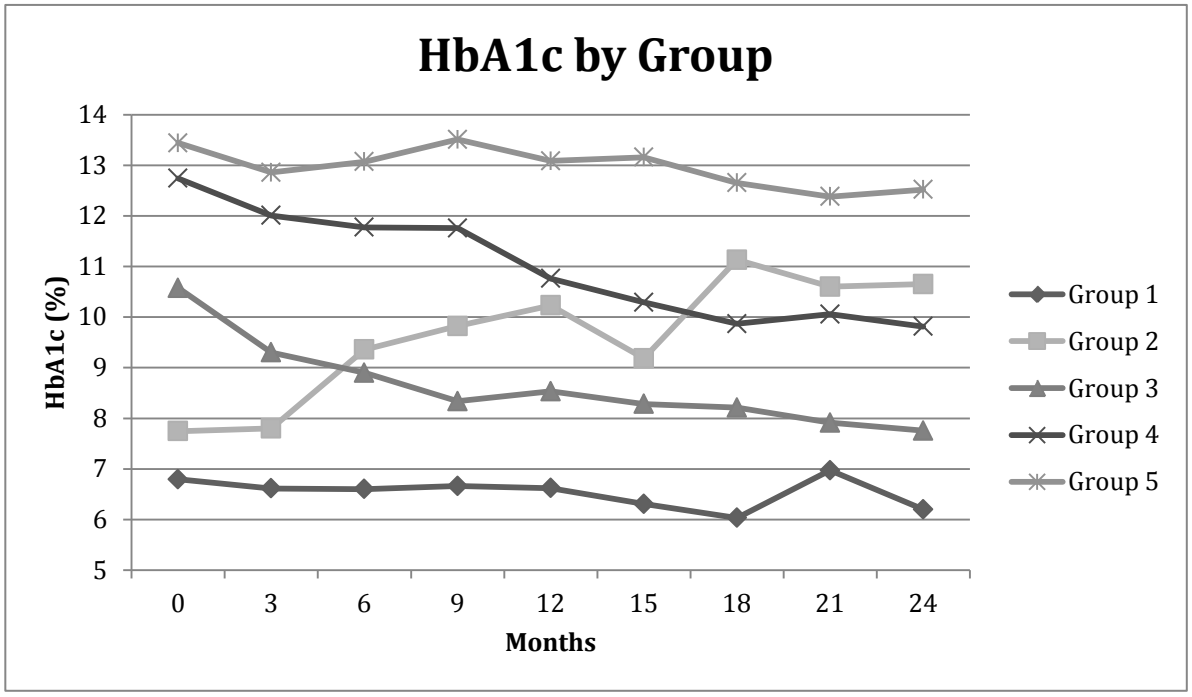


Figure 3. HbA1c Groups, as identified by trajectory analysis. A total of five different groups were identified. Group 1 N=16 (8.0%), Group 2 N=17 (8.4%), Group 3 N=54 (26.9%), Group 4 N=64 (31.8%), Group 5 N=50 (24.9%).

5.0 PREVALENCE AND INCIDENCE OF CLINICALLY RECOGNIZED CASES OF TYPE 1 DIABETES IN CHILDREN AND ADOLESCENTS IN RWANDA, AFRICA

To be submitted for publication

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5.1 ABSTRACT

AIMS: To determine prevalence and incidence estimates for documented (clinically recognized) cases of T1D in the Life For a Child Program (LFAC) (with onset ≤25 years) from six representative districts and the capital of Rwanda.

METHODS: Cases were identified from the LFAC/ARD registry and visits to district hospitals. Denominators were calculated from district level population surveys. Period prevalence data were collected from August 1, 2011 through July 31, 2012 and annual incidence rates were calculated, retrospectively, from 2004-2011. 95% confidence intervals were calculated using a Poisson distribution.

RESULTS: The prevalence of known T1D in seven districts in Rwanda for ages 0-25 years was 16.4 [14.6-18.4]/100,000 (0-15 years 4.7[3.5-6.1]/100,000), which was significantly lower than other regional reports. Prevalence was higher in females (18.5[15.8-21.4]/100,000) than males (14.1[11.8-16.7]/100,000; P = 0.01) and rates increased with age. The annual incidence rate ranged from 0.79 [0.4-1.4]/100,000 in 2004 to 2.7[2.0-3.6] /100,000 in 2010, a 4 fold increase. Incidence rates were higher in females than males.

CONCLUSIONS: Our report of known cases of T1D shows lower rates in Rwanda than the US and the limited data from other African Countries. Incidence of recognized cases has increased over time, but has recently stabilized. However, the likelihood of missed cases due to death before diagnosis and misdiagnosis is high and therefore more definitive studies are needed.

5.2 INTRODUCTION

Diabetes is an emerging problem in developing countries as they move through the epidemiological transition,[1] and an estimated 18.7million people in sub-Saharan Africa will be affected by this disease by 2025.[2] Type 1 diabetes is one of the most frequently seen non-communicable disease (NCD) in children and should therefore be of great and increasing importance to public health officials,[28] especially those in developing countries where access to insulin is low.[89]

The global incidence of type 1 diabetes (T1D) is rising 3% annually, but geographic variations are known to occur.[2,14,15] Unfortunately the true burden of this disease in Africa is not clear, as there are currently very few prevalence and incidence studies, especially of T1D in children and young adults. Only three prevalence studies[23,29,30] and five incidence surveys[22,26,30–32] focus on the rates of T1D in this age range, and none have been within the last 10 years. The prevalence rates in these countries range from 27/100,000 in Algeria (for ages 0-15 years),[30] to 95/100,000 in Sudan (for ages 7-14 years),[23] and incidence rates range from 1.5/100,000 in Tanzania (ages 0-19 years),[31] to 10.1/100,000 in Sudan (ages 0-15 years),[22] highlighting the geographic variation in these rates. Additionally, these studies are from primarily Arab countries, and therefore provide little information on what rates may be in sub-Saharan countries.

There have been no such prevalence studies in the East African country of Rwanda, even though diabetes awareness and support has increased in recent years.[118] Prevalence estimates that have been previously reported for Rwanda are extrapolated from studies from “similar” populations, but this is an imprecise process and most likely results in inaccurate rates of T1D in this country.[2]

In Rwanda, there are 41 district hospitals and 400 health centers with 0.05 physicians and 0.42 nurses per 1,000 citizens.[137] Specialized diabetes care and supplies are often not available. To address this gap, the International Diabetes Federation's Life For a Child (LFAC) program, which is managed by the Australian Diabetes Council and HOPE *worldwide,* has been working since 2004 with the Association Rwandaise des Diabetiques (ARD) based in Kigali, by donating insulin, glucose monitoring supplies, education materials, and specialist training. Due to the overall limited access to insulin and prohibitively high prices, almost all diabetes cases are referred to the ARD for assistance. To receive assistance, children and adolescents must register with the LFAC program and have, at minimum, a yearly clinic evaluation. The ARD currently provides care to patients in Kigali and over half of the district hospitals in Rwanda.

To assist in closing this gap in prevalence and incidence knowledge, yet recognizing this report is not a full epidemiologic study, we present prevalence and incidence estimates for documented (clinically recognized) cases of T1D in youth and adolescents ($\leq$25 years) from six representative districts and the capital, Kigali City, of Rwanda. We also compare these rates to those of other countries from the region and the US.

5.3 METHODS

This report comprises data from a quality improvement project of the LFAC Program in collaboration with the ARD and GSPH. The University of Pittsburgh's IRB determined that this project was exempt from review under the "Existing Data" category.

5.3.1 Study Population

All participants of this project are registered in the Rwanda LFAC program which was started in 2004. To be enrolled, participants must be citizens of Rwanda aged 25 years and younger needing assistance with obtaining insulin and other diabetes supplies.

Selection of Districts

The districts for this report were selected based on the following characteristics: ability to determine the size of the less than 26 year population, at least one district hospital where diabetes patients in that district would go for care that are currently being serviced by the ARD/LFAC program. Table 10 lists the selected districts and their hospitals.

5.3.2 Case Ascertainment

To identify cases, we used a combination of data extracted from the previously documented cases from the LFAC registry and data collected from new patients identified during our visits to the selected district hospitals. Age, date of birth, date of diagnosis and district of residence data were extracted from LFAC clinical charts. We believe we have covered all sources of insulin (primarily ARD and district hospitals) available to residents in those districts, excluding only those who obtained insulin from outside of the country, a practice we believe to be minimal. Unfortunately, hospitals do not keep official records on diagnosed cases of diabetes. Capture/recapture was not therefore possible as no other secondary source was identified. Yearly incidence estimates were based on self/family reported year of diagnosis and was not verifiable by hospital or other medical records.

Overlapping catchment

To maximize case identification for each district we also visited hospitals from the neighboring districts. Only patients who physically lived in a district of interest (or lived there when they developed diabetes) were included for this project. Those who were identified as new cases, but did not live in a selected district, were added to the LFAC registry for further follow up.

Population denominators

In 2006 the Rwandan government underwent a district re-alignment and the country is now divided into 4 Provinces plus Kigali City, 30 Districts, 416 Sectors, 2,148 Cells, and 14,837 Villages. To account for the new division of the population, a census/survey was initiated for each district in 2006.[138]

The population of each District was reported for males, females, and overall, in 5 year age groups (ex. 0, 1-4, 5-9, 10–14, etc.). Therefore, we summed the 0-24 year age ranges, and then to account for those aged 25 years, we calculated the number of 25-29 year olds that were 25 years using the percentage (23%) of 25-29 year olds that were 25 years in the Population Projection data.[139]

No data were available for the Eastern Province (Rwamagana) from this survey; however, the local government soon after performed their own mini-census.[140] Population data were also presented in age groups, however these were not as uniform (<1, 1-5, 6-13, and 14-35). To account for this, we summed the population counts for 0-13 years and then calculated the number of those who were 14-25 years from the 14-35 year age group, again using the appropriate percentage (46%) from the Population Projection data.[139,140]

The calculated populations for 2006 were then used as a base for estimation the annual population for each year from 2004-2012, by assuming a 2.8% increase/decrease in population

for each subsequent/previous year, which is consistent with data from the Population Projection data and censuses.[139]

5.3.3 Data Analysis

All data were de-identified and entered into an electronic database. Period prevalence rates were calculated using identified cases that were under age 26 years between August 1, 2011 through July 31, 2012 and the mean population of years 2011 and 2012. Annual incidence rates were calculated using the number of self-reported diagnosed cases for each year (2000-2011) over the estimated population ($\leq$25 years) for that year. Cases from 2012 were not included in incidence calculations as data collection stopped as of July 2012. 95% confidence intervals for rates were calculated using a Poisson distribution. Demographic data (poverty rate, percent ever attended school, literacy rate, percent orphans, percent of homes with phones or radios, mean distance from health center, employment rates) for each district were also examined for associations with rates as possible mediators of within-country variation.[141]

Mean and standard deviation of age at diagnosis were calculated for the overall population, and by district, by sex and by age group. Statistical comparisons of age at diagnosis were completed using t-tests and ANOVAs and chi square test comparisons were used to compare rates. A nominal p-value of $P < 0.05$ was used to denote significance.

The expected number of total type 1 diabetes patients was calculated by applying our estimated prevalence rate to the total population under 26 years (or 0-15 years) of age in Rwanda.

The analysis for this paper was generated using SAS/STAT software, Version 9.3 of the SAS System for Windows, copyright © 2011 SAS Institute Inc.

5.4 RESULTS

5.4.1 Prevalence

A total of 306 type 1 diabetes cases (under age 25 years) were identified in Rubavu (N=17), Gakenke (N=37), Rusizi (N=36), Huye (N=28), Rwamagana (N=21), Muhanga (N=41) and Kigali (N=126) from August 1, 2011 through July 31, 2012 (table 11). The mean overall age at diagnosis was 15.1±5.0 years, and ranged from 14.4±5.5 years in Muhanga to 16.5±5.5 in Rusizi. Prevalence estimates range from 7.5 [4.4-12.0]/100,000 in the North-Western District, Rubavu, to 22.1 [18.4-26.3]/100,000 in the Capital City of Kigali (table 11). Surprisingly, the Southern District of Muhanga also had a high prevalence (20.1 [14.4-27.2]/100,000) - close to that of the urban Kigali setting. The overall crude prevalence of type 1 diabetes in Rwanda for 0-25 years was thus estimated to be 16.4 [14.6-18.4]/100,000 (prevalence for 0-15 years was 4.7[3.5-6.1]/100,000).

Prevalence rates of type 1 diabetes were significantly higher in females (18.5[15.8-21.4]/100,000) than males (14.1[11.8-16.7]/100,000) overall (p = 0.01) (table 11). The same trend was seen in each district except for Rubavu and Huye, which had higher rates for males. However, only the Gakenke District had a significant difference between the sexes (6.7 [3.1-12.8]/100,000 males; 18.8[12.4-27.4] /100,000 females, p=0.003) (table 11). There were no significant differences (p=0.40) by sex in mean age at diagnosis overall or by district (data not shown).

Prevalence rates increased with age (Supplemental table 3; Appendix B). The lowest prevalence was for the 1 – 4 year age group (0.6 [0.07-2.1]/100,000), while the highest was for

the 20 – 24 year age group (54.1 [46.0-63.1]/100,000). For Rusizi and Muhanga Districts, the 25-year age group had the highest prevalence rate (Rusizi 84.8 [31.1-183.8]/100,000; Muhanga 79.3 [25.4-185.5]/100,000), while Rubavu, Gakenke, Huye and Kigali City had the highest prevalence rates in the 20 – 24 year age group (Rubavu 33.3 [16.6-59.6]/100,000; Gakenke 43.4 [23.6-72.9]/100,000; Huye 50.1 [28.0-82.5]/100,000; Kigali City 50.7 [39.0-64.9]/100,000). Only two cases were identified in the 1 – 4 age group, both from Kigali. In the Rwamagana district, only one case was identified in the 6 – 13 year age group (1.9 [0.04-10.5]/100,000), while the rest were in the 14 – 25 year age group (46.0 [27.6-72.0]/100,000) (data not shown). The only district demographic variable that was correlated with prevalence was the percent of those who ever attended school, but this was only of borderline significance (r=0.74, p=0.054).

5.4.2 Incidence

A total of 260 registered cases of type 1 diabetes in youth under age 26 years were diagnosed from 2004 - 2011 in these selected districts (an additional n=93 cases were diagnosed prior to 2004 or had unknown diagnosis dates). The annual incidence rate from 2004 to 2011 ranged from 0.79[0.4-1.4]/100,000 in 2004 to 2.7[2.0-3.6]/100,000 in 2010 (table 13), a 4 fold variation. Overall incidence rates were higher in females than males, except for 2005- 2007. However, the only significant sex differences were in 2010 (1.9 [1.1-3.1]/100,000 for males; 4.0 [2.7-5.6]/100,000 for females, p=0.004) and 2011 (1.5 [0.8-2.6]/100,000 in males; 3.4 [2.2-4.9]/100,000 for females, p=0.04) (table 13).

Annual incidence rates increased over time, with the highest rates seen in the older age groups in more recent years (Supplemental Table 4; Appendix B). The highest incidence rate,

however, was seen in 2008 for those aged 15-19 years (8.1 [5.0-12.4]/100,000). Sample size was too small and our timeline too short to perform any age-period-cohort analyses at this time.

5.5 DISCUSSION

Our report of known cases of T1D in Rwanda suggests that the prevalence may be significantly lower in Rwanda than other African countries[23,29,30] and less than a tenth of those for US African Americans.[11] Though incidence of recognized cases has increased over time, it has recently stabilized at a rate similar to that reported in Tanzania in 1991. However, the likelihood of missed cases due to death before diagnosis and misdiagnosis is high, suggesting that our results are an underestimation of the true burden of this disease, while early mortality may also distort the yearly incidence estimates from the early years.

5.5.1 Prevalence

The overall crude prevalence rate of type 1 diabetes in Rwanda, for those aged 25 years or less, is 16.4 [14.6-18.4]/100,000. This rate ranged from 7.5/100,000 in the rural district of Rubavu to 22.1/100,000 in Kigali City. These estimated rates are significantly lower than previous prevalence studies from sub-Saharan Africa and the US (table 12). The estimated prevalence rates in Rwanda are 11x lower than the Sudan, 3x lower than Nigeria, 6x lower than Algeria, 47x lower than African Americans aged 0-9 years, and 11x lower than African Americans aged 10-19 years.[11,23,29,30]

There were, however, some major differences between our study and the previous work that could have contributed to such differing prevalence rates. The studies from Sudan[23] and

Nigeria[29] were surveys given to schoolchildren asking about diabetes symptoms, not hospital surveys as ours was. While the prior studies allowed for identification of previously unknown cases, our methodology limited our cases to those who are clinically recognized and recorded in the LFAC registry. Using only the previously known cases in Sudan and Nigeria (excluding those newly identified by screening), the prevalence rates decreased to 78.8/100,000 and 17.8/100,000 respectively.[23,29] These rates are considerably closer to those in Rwanda – especially for Nigeria, which is only 1.8X higher when only considering previously known cases. This suggests that if we had the ability to screen for cases, our rates may be more similar to the previous reports. However, a school based survey also has weaknesses and biases and may not truly reflect national prevalence either, in countries with relatively low school attendance as in Rwanda. Attendance for a cohort of T1D patients in Rwanda has been reported to be 51.4%, suggesting that a school survey would have resulted in many missed cases as well.

As with other studies from sub-Saharan Africa,[23,28,29] the prevalence rate in Rwanda increased with age (Supplemental Table 3; Appendix B), and was higher in females (table 11). Similar sex differences (females 112/100,000; males 79/100,000) and increases in prevalence with age were seen in Sudan.[23] Nigeria also had increasing rates with age (3/100,000 for those aged 5 – 9.99 years to 74/100,000 in those aged 14-17 years). However, the Nigeria study was different from ours as they saw an opposite pattern by sex, with males having a higher crude prevalence rate (38/100,000) than females (25/100,000).[29] In Ethiopia, the mean age at diagnosis was 10.1 years (for those diagnosed before age 15 years), while in Sudan there was a bi-modal distribution with peaks at 14 and 7 years.[28] Similarly, the mean age at diagnosis for a likewise aged population in our study was 11.1±3.9 years. Trends in age at diagnosis suggest that cases

are being detected at earlier ages than previously, possibly due to increased knowledge of diabetes and its symptoms.

5.5.2 Incidence

Our inability to screen for new cases and thus, dependence on clinically diagnosed cases, and our reliance on self-reported dates, and the high likelihood of missed cases because of pre or post diagnosis mortality may have affected our incidence rates. The annual estimated incidence rate ranged from 0.79[0.4-1.4]/100,000 in 2004 to 2.7[2.0-3.6] /100,000 in 2010. Comparing annual incidence rates of comparable age ranges to previously estimated incidence rates in Africa, the rates in Rwanda are lower than rates seen in Sudan, Tunisia, Libya and Algeria (table 12).[22,26,30,32] The incidence rates in 2011, however, are similar to the annual rate in Tanzania from 1979-1988.[31] In comparison to US African American incidence rates, the rate in Rwanda for those 0-9 years is 1/63 of the rate in the US, and ¼ of the rate for those 10-19 years in the US (table 12).[11]

Methodological differences may again have contributed to the lower incidence rates in Rwanda, as several of the prior studies were based on data from national or province registries (Algeria[30], Tunisia[26] and Libya[32]), while we were limited to only cases reported to the LFAC registry. However, the generalizability of the previous studies is also limited, as the majority of them were for only one city or a few districts in each country and they were located in predominantly urban areas. It is of particular note, that the country located the closest to Rwanda and with the most similar ethnic background– Tanzania – has the most similar incidence rate.

Incidence rates also increased over time in our population - a pattern seen globally[14,15] and locally in sub-Saharan Africa [Sudan (5.9/100,000 in 1987 to 10.1/100,000 in 1992)[22], Libya

(7.0/100,000 in 1981 to 7.8/100,000 in 1990)[32], and Algeria (1.6/100,000 in 1981 to 8.1/100,000 in 1998)[30]]. There were no significant changes over the 5-year study in Tunisia,[26] and no time trends were reported for Tanzania.[31] The only country that found a significant difference by sex was Libya, where females had a higher incidence (9.1/100,000) than males (6.6/100,000).[32] In Tunisia incidence was lower in those aged 0-4 years (3.3/100,000) than those 10-14 years (11.5/100,000)[26] and similar increases with age were seen in Tanzania (0.5/100,000 for 5-9 years, 2.2/100,000 for 10-14 years, and 3.4/100,000 for 15-19 years).[31]

Even though the hospitals in Rwanda are visited on a quarterly basis, due to high nurse turnover, long travel distances for patients, lack of scheduled consultations, and continued utilization of traditional healers, it is likely that some known cases are not recorded. A failure to diagnose diabetes in fatal cases further complicates the situation, for as shown in a previous study in Tanzania, 21 of 199 patients diagnosed with cerebral malaria actually had coma due to uncontrolled diabetes.[142] Another study in Tanzania found that poor record keeping along with low awareness can lead to misdiagnosis of diabetes.[143] Of 35 people who presented with diabetic ketoacidosis, no diabetes symptoms were recorded in over 40% of patients after their referral visit or a visit to the casualty department, and a correct diagnosis for only 13 of 33 (39.4%) people was made at the referral level, and only 37.1% (n=13/35) at the casualty department. It is highly likely that children with type 1 diabetes in Rwanda died before they were formally diagnosed. This is supported by the low incidence at younger ages in our population and the knowledge that until 2009, most district hospitals did not have a glucose meter available to them. Additionally, anecdotal reports have shown that some children/adolescents in Rwanda have an apparent ability to survive with high HbA1c levels and little to no insulin. It is therefore possible that there are undiagnosed children and adolescents living relatively normal lives.

Typology was not used to confirm diagnosis in any of these studies. While we believe that the majority of our cases are type 1 based on age at onset and their dependence on insulin, no formal antibody or c-peptide testing was available. Therefore, it is possible that some cases are actually type 2 or another form of diabetes. Additionally, diagnosis dates were often self-reported and were sometimes unknown.

While there are thus several reasons that case reporting may be low in Rwanda, district hospitals and the ARD are where diabetes patients will likely seek, or be directed for, care. Even those who can afford insulin are referred for clinical consultations and management guidance. Therefore, we believe that we have a fairly representative cohort of known T1D cases in Rwanda through use of routinely collected clinical data. Thus, it is possible that rates of type 1 diabetes in Rwanda are truly lower than expected. As previously mentioned, geographic variations in general have been identified[14,15] which may span a range of 350 fold. The cause of this variation, derived from standardized registry data, is likely due to a combination of genetics, environment, and autoimmune factors.[7] The previous African studies were in primarily Arab countries, which have been shown to have very high rates of diabetes.[2,14,15] Since the percent of the Arab population in Rwandan is significantly lower than these countries, one might expect to see much lower rates of diabetes in Rwanda. This is further supported by the fact that the data from Rwanda most closely matches the data from Tanzania. Unfortunately, genetic testing was not available at this time, however, this should be considered in future studies as differences in the distribution of specific genes (ex. HLA-DQ_{β}) have been implicated in the geographic variation in rates of type 1 diabetes.[144]

Early exposure to cow's milk has also been linked to the global differences in diabetes rates,[145,146] as increased consumption of cow's milk is associated with increased incidence of

type 1 diabetes. In previous Demographic and Health Surveys, reported rates of exclusive breastfeeding are higher in Rwanda (91.4% for 0-1 months to 75.7% for 4-5 months) than, for example, Nigeria (2.1% for 0-1 months to 0.1% for 4-5 months) and Tanzania (55.2% for 0-1 months to 8.0% for 4-5 months).[147–149] Higher rates of prolonged breastfeeding in Rwanda might, therefore, translate to lower T1D risk.

Despite the high probability of under-ascertainment and the non-formal epidemiologic analysis, this first survey of known T1D cases in youth and adolescents in Rwanda suggests that the local rates are lower than those of other African countries and US African Americans. Estimates of rates of this disease are needed to ensure that necessary support is being provided for these countries where insulin and other management necessities are hard to obtain. Based on our estimates, there may be 1,192 T1D cases under the age of 26 years in Rwanda (95% CI 1,061-1,337) (239 under 15 years (95% CI 178-309)), each of which will require guidance and additional healthcare over their lifetime. However, due to the high likelihood of missed cases due to death before diagnosis and misdiagnosis, more definitive studies are needed to determine if our estimates are true or an underestimation due to missed cases.

5.6 TABLES

Table 10. Table of selected districts and their associated hospitals.

Region of Country	District	Hospitals in District
North West	Rubavu	Gisenyi
South West	Rusizi	Gihundwe, Mibirizi
Central South	Muhanga	Kabgayi
Far South	Huye	CHUB, Kabutare
North	Gakenke	Nemba, Ruli
East	Rwamagana	Rwamagana

Table 11. Prevalence estimates (per 100,000) of clinically diagnosed type 1 diabetes in six districts and Kigali City, Rwanda, overall and by sex.

	25 and under	Cases	Overall Prevalence (95% CI)	Age at Diagnosis	Males (95% CI)	Females (95% CI)
Rubavu	227,556	17	7.5 (4.4-12.0)	14.6±5.2	9.9 (5.0-17.8)	5.1 (1.9-11.1)
Gakenke	277,103	37	13.4 (9.4-18.4)	15.3±4.2	6.7 (3.1-12.8)	18.8 (12.4-27.4)*
Rusizi	266,724	36	13.5 (9.4-18.7)	16.5±5.5	11.0 (6.1-18.1)	16.1 (10.0-24.7)
Huye	183,028	28	15.3 (10.2-22.1)	16.2±4.8	15.5 (8.4-26.0)	15.1 (8.2-25.3)
Rwamagana	136,253	21	15.4 (9.5-23.6)	16.1±3.9	14.9 (7.1-27.4)	14.4 (6.9-26.6)
Muhanga	204,092	41	20.1 (14.4-27.2)	14.4±5.5	16.0 (9.1-26.0)	24.0 (15.5-35.4)
Kigali	569,587	126	22.1 (18.4-26.3)	14.5±5.1	19.3 (14.5-25.1)	24.9 (19.4-31.5)
Total	1,864,342	306	16.4 (14.6-18.4)	15.1±5.0	14.1 (11.8-16.7)	18.5 (15.8-21.4)*

* Denotes significantly different rate from males at $p<0.05$

Table 12. Prevalence and incidence estimates (per 100,000) of clinically diagnosed type 1 diabetes in other countries compared to similarly aged Rwandan populations.

Population (age)	Study Year(s)	Prevalence/ 100,000	Prevalence/ 100,000 In Rwanda (95% CI)	Incidence/ 100,000	Incidence/ 100,000 In Rwanda (2011) (95% CI)
Sudan (7 – 14 years)	1987	95	8.7 (6.3-11.8)	-	-
Nigeria (5 – 17 years)	1990	33	10.0 (7.9-12.3)	-	-
Algeria (0 – 15 years)	1979 - 1988	27	4.7 (3.5-6.1)	4.4	1.3 (0.7-2.2)
US African Americans (0 – 9 years)	2001	57	1.2 (0.6-2.3)	15.7	0.25 (0.03-0.9)
US African Americans (10 – 19 years)	2001	204	18.6 (15.2-22.5)	15.7	4.0 (2.6-6.1)
Sudan (0 – 15 years)	1987 - 1990	-	-	10.1	1.3 (0.7-2.2)
Tunisia (0 – 19 years)	1990 - 1994	-	-	6.95	1.8 (1.2-2.7)
Libya (0 – 14 years)	1991 - 2000	-	-	8.3	1.1 (0.6-2.0)
Tanzania (0 – 19 years)	1982 - 1991	-	-	1.5	1.8 (1.2-2.7)

Table 13. Annual incidence estimates (per 100,000) of clinically diagnosed type 1 diabetes, overall and by sex.

Year	New Cases	Overall Rate (95% CI)	Males (95% CI)	Females (95% CI)
2004	12	0.79 (0.4-1.4)	0.40 (0.08-1.2)	1.4 (0.6-2.6)
2005	23	1.5 (0.9-2.2)	1.8 (1.0-3.0)	1.3 (0.6-2.5)
2006	21	1.31 (0.8-2.0)	1.5 (0.8-2.6)	1.3 (0.6-2.4)
2007	39	2.4 (1.7-3.2)	3.1 (2.0-4.5)	2.0 (1.1-3.3)
2008	41	2.4 (1.7-3.3)	2.0 (1.2-3.2)	3.3 (2.1-4.8)
2009	35	2.0 (1.4-2.8)	1.7 (1.0-2.9)	2.6 (1.6-4.1)
2010	48	2.7 (2.0-3.6)	1.9 (1.1-3.1)	4.0 (2.7-5.6)*
2011	41	2.2 (1.6-3.0)	1.5 (0.8-2.6)	3.4 (2.2-4.9)*

* denotes significantly different rate from males at $p<0.05$

6.0 NATURAL PROGRESSION OF TYPE 1 DIABETES PATIENTS ENROLLED IN THE RWANDA LFAC PROGRAM FROM 2004-2011

To be submitted for publication

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6.1 ABSTRACT

AIMS: To report on the natural history of type 1 diabetes (T1D) for the first 500 cases in the Life For a Child (LFAC) program in Rwanda from 2004 – 2011. We present information on: program utilization, losses to follow up, complications, and mortality.

METHODS: Participants were children and youth (diagnosed $\leq$ 25 years) enrolled in the LFAC program before 2011. The number and frequency of visits and HbA1c testing was determined, while vital status was assessed as of Nov 1, 2011. Participants not recently seen or located were censored as of their last visit. Mortality rates were calculated for those with known vital status (n=361).

RESULTS: Of the first 500 participants, 54.8% (n=270) were female and 45.2% (n=233) were male. Mean age at last visit and mean duration of diabetes were 20.5±4.7 years and 4.9±3.2 years, respectively. Five-year survival was 93.8 while crude mortality was 6.9% (25/361; 95% CI, 4.5 – 10.2%) or 13.9/1,000 (95% CI 9.0-20.6/1,000) person years of diabetes, and was directly associated with age at diagnosis, and inversely to year of first visit, BMI, and monitoring frequency. However, since vital status is unknown for 134 participants, mortality could be as high as 32.1% or 40.2/1,000 person years of diabetes.

CONCLUSIONS: These data demonstrate that mortality associated with T1D in Rwanda is similar to other African T1D populations, but higher than in developed countries. Delayed diagnosis of T1D may be contributing to this excess risk, but improvements in survival over time suggest that advancements are being made. Hypertension and early development of complications remain issues and need to be addressed. Additionally, we hope that by identifying and addressing barriers to care will lead to more thorough and timely care in the future.

6.2 INTRODUCTION

Diabetes is a disease of growing concern in the developing world. An estimated 18.7 million people in Africa will be affected with diabetes by 2025,[2] posing a potentially large problem for a population that already has limited access to healthcare. In order for a person with type 1 diabetes (T1D) to survive and prevent complications, they need access to the necessary insulin and other glucose testing supplies.[60] However, this necessary care is often not accessible in African populations.[89]

Help for these countries usually come in the form of external support. One such program is the Life For a Child (LFAC) program, which is managed by the International Diabetes Federation in conjunction with the Australian Diabetes Council and HOPE *worldwide*. LFAC's mission is to support the provision of the best possible diabetes healthcare, given local circumstances, by supplying children and adolescents ($\leq$ 25 years) in developing countries with the necessary insulin, and glucose testing supplies, and with HbA1c testing capability. The program also offers diabetes education, and advanced training and advice to both patients and local healthcare providers. The only requirement for those supported by the program is that they complete yearly LFAC clinical examinations that include, when possible, laboratory measures such as HbA1c and albumin/creatinine ratios.

The Association Rwandaise des Diabetiques (ARD) is a diabetes association located in Kigali City, Rwanda, that receives support from the LFAC program. The program there was initiated in 2004 with 25 children, and has expanded over the years and now provides support for over 630 children. HbA1c testing was first made available to the ARD by the University of Pittsburgh's Graduate School of Public Health (GSPH) in the summer of 2009. [118] At that time, Quarterly Review clinical visits were also added to the regular practices of the ARD in order to

provide the staff access to more timely and representative information to enable them to make better and more informed adjustments to each patient's management regimen.

The short-term effects of these additions have been previously reported,[118] but little is known concerning the natural progression of the disease in the members of the Rwanda LFAC program who have been enrolled since its inception. In order to provide the best care to their patients, it is also helpful to document participants that have been lost to follow up, so as to identify the barriers to receiving ARD care, or alternatively, to identify other care options in order to not duplicate efforts.

The objective of this report is, therefore, to follow up to 8 years, the first 500 cases registered with the ARD from 2004 – 2011. We report on the natural history of T1D in Rwanda by presenting information on: utilization of the LFAC program (number and frequency of visits), losses to follow up, clinical characteristics, laboratory measures, complications, and mortality.

6.3 METHODS

This report comprises data from a quality improvement project of the LFAC Program in collaboration with the ARD and GSPH. The University of Pittsburgh's IRB determined that this project was exempt from review under the "Existing Data" category.

6.3.1 Study Population

This report focuses on the first 500 children and youth enrolled in the LFAC program from 2004 -2011. All participants of this program evaluation are registered participants of the Rwanda LFAC program. To be enrolled, participants must be citizens of Rwanda, aged 25 years or

younger, needing assistance with obtaining insulin and other diabetes supplies. Participants either sought care from the ARD or were referred by their healthcare provider.

6.3.2 Data Collection

Data were extracted from several different clinical forms. The first version of the LFAC annual form was used from 2005-2007. Data on sex, district, date of birth, diagnosis date, insulin regimen, glucose monitoring frequency, height, weight, systolic and diastolic blood pressure (BP) and frequency of reported yearly clinic visits were extracted from these forms. These LFAC forms were later condensed to a one-page form that has been used since 2008. The above data, along with tuning fork vibratory sensation and monofilament response tests, HbA1c, and albumin creatinine ratios (A/C ratios) were extracted from these forms. In 2009 use of a Quarterly Review form was also implemented to document interim visits and allow for additional data collection. Data on glucose monitoring frequency, insulin regimen, height, weight, systolic and diastolic BP, HbA1c and A/C ratio (when required) are recorded on these forms. Clinical data and vital status were extracted through December 2012. No data were collected for research purposes as all data reported are routinely recorded for clinical care purposes.

6.3.3 Laboratory data

Blood (finger prick) and urine (spot samples) were collected from each patient and processed on the Siemens DCA Vantage^{TM} (which reports DCCT equivalent values) by University of Pittsburgh Graduate School of Public Health MPH students (who visit annually to assist in this

process) or ARD staff. Data for HbA1c and A/C ratio were collected from these samples. The maximum HbA1c value for this machine is ">14 % (>130 mmol/mol)," so for data analysis purposes these results were reported as "14.1% (131 mmol/mol)." The inter-assay CV range for the HbA1c measures was from 2.1% to 3.8% during the data collection.

6.3.4 Complication Assessment

Neuropathy

Neuropathy was defined as failure to feel a 10g monofilament (less than seven of ten correct responses) on the dorsum of the great toe and/or failure to feel vibration from a 120Hz turning fork placed on the dorsum of the great toe for 10 seconds. [123]

Microalbuminuria

Microalbuminuria (MA) was defined as an albumin/creatinine (A/C) ratio of 30-299 mg/g in a spot urine sample, and overt nephropathy as an A/C ratio $\geq$ 300 mg/g.

Hypertension

Hypertension was defined as having systolic BP $\geq$130 mmHg or diastolic BP $\geq$80 mmHg or a history of BP medication. The percent of those using BP medication, however, is low due to limited availability.

6.3.5 Utilization Assessment

All previous clinical records were analyzed to determine number and frequency of visits and HbA1c testing for each participant. We attempted to contact participants who had not recently (within the last 15 months i.e. since November 1, 2011) attended clinic either by phone, through

contacts at the local hospital, or by further investigation by a forensic epidemiologist (WR). Those who were not able to be located were deemed to be “lost to follow up” and were censored as of their last clinic visit.

6.3.6 Vital Status Assessment

Vital status was determined through clinic attendance, deaths reported to the ARD, hospital surveys, and additional follow up by a forensic epidemiologist. For crude mortality estimates, vital status was assessed as of November 1, 2011. A participant was considered to be alive if: he/she had attended clinic between November 1, 2011 and December 31, 2012, he/she was known to be alive by other contact with hospital staff or other participants, or he/she was determined to be alive after investigation by a forensic epidemiologist. Autopsies are not customary in Rwanda and death certificate data is likewise sparse. Thus, cause of death for this cohort were collected through contact with local hospitals and communications with families, but is limited in both quality and completeness.

6.3.7 Data Analysis

Descriptive statistics, including mean, standard deviation and frequencies were calculated for clinical and utilization data. ANOVA, two-sample and paired t-tests were used for comparisons of continuous variables, while X^2 tests and Fisher’s Exact tests were for comparisons of categorical varibles. Tukey’s HSD test was used for any post-hoc pairwise comparisons. A p-value of 0.05 with appropriate Bonferroni corrections was used to assess significance for

multiple comparisons. Time between visits was calculated assuming that a year had 365.25 days and a month had 30.44 days.

An overall crude mortality rate was calculated for this cohort and cause-specific mortality was assessed where possible. Person years of diabetes were calculated for those with known vital status (n=361; total known person years of diabetes = 1,792 years). For those with unknown vital status, person years of diabetes were calculated as of last known follow up. Ninety-five percent confidence intervals were computed assuming a Poisson distribution. Kaplan-Meier curves were constructed to estimate cumulative survival and Log-rank tests were used to test for significant differences in survival between sub-groups. Cox regression models were used to examine differences in survival for all continuous demographic and clinic variables, as well as simultaneously adjusting for multiple variables (Model 1). The proportional hazards assumptions of the models were confirmed by testing time-dependent interaction variables. All hazard ratios (HRs) are reported per increase of 1 unit of measure.

All statistical analysis was performed using SAS 9.2 (SAS Institute, Cary, NC) statistical software.

6.4 RESULTS

Of the first 500 LFAC participants, 54.8% (n=270) were female, 45.2% (n=233) were male, and seven were of unrecorded sex. Mean age at last visit (range June 2009 – December 2012) was 20.5±4.7 years when mean duration of diabetes was 4.9±3.2 years. Only 18 (3.8%) of participants were diagnosed before age 5 years, while 186 (39.3%) were diagnosed between the ages of 15-19 years (figure 4). Twenty three percent (n=114) were 25 years or older as of 2012,

and will no longer be eligible for support from LFAC in the next year (n=39), or already are not (n=75). Fifty two (10.5%) were from the Eastern Province, 57 (11.5%) from the North, 84 (16.9%) from West, 123 (24.8%) from Kigali, and 180 (36.3%) were from the South.

Within the last year (since November 1, 2011), 319 (63.8%) of the first 500 participants, have been seen. Of the 181 (36.2%) who have not been seen, 33 are known to have died, 5 are known to be duplicate IDs, and 17 are known to be alive (figure 5). Forty of those not seen in the last year are 26 years or older and have, thus, aged out of the LFAC program. The most common reasons for non-attendance (from those we later contacted by phone or forensic epidemiologist) were: being away at boarding school (n=4), lack of transport (n=3), sick on day of visit (n=3), did not hear radio announcement (n=2), were pregnant (n=2), or no longer believed they had diabetes (n=2).

6.4.1 Utilization

Since the beginning of the LFAC program, 2,411 clinic visits have been recorded for the first 500 participants (271 during 2005-2008; 2,140 for 2009-2012). A total of 488 (97.6%) participants have attended at least one recorded clinic visit, while 12 were registered by name only (no demographic or clinical data). These participants received insulin, but never completed a full clinic visit. Visit frequency has increased over the last several years (n=23 in 2005; n=763 in 2012), as has utilization of HbA1c testing (n=170 in 2009; n=629 in 2012). Seventy-seven (15.4%) participants had not attended a clinic visit since 2008 and 53 (10.6%) had only one visit from 2009-2012, while 370 (74.0%) had multiple visits from 2009-2012 (table 14). Those who had only one visit from 2009-2012 were significantly older than those with multiple visits and were diagnosed at an older age than participants with no visit (table 14). A larger percentage of

people from the North province attended multiple visits (84.2%) compared to those in other provinces, but this was not significantly different.

A total of 1,883 HbA1c tests have been recorded. Eighty two percent of the first 500 (n=409) have had at least one HbA1c measurement, with a mean number of HbA1c tests per person of 4.6±2.5 (range 1-11). For those with multiple measurements, the mean time between tests was 6.1±4.6 months. Several (14.2%) tests were taken more frequently than the recommended 3 months, while other tests (26.1%) were taken more than 6 months apart. For those with multiple clinic visits, the average time between visits was 5.7±4.6 months. Some participants attended clinic multiple times within 3 months (17.8% of visits), while others waited longer than 6 months (24.7% of visits). The mean number of visits for each person was 5.1±2.8 (range 1-12 visits). For those with multiple visits, mean HbA1c decreased significantly from 11.1±2.7%, at first visit, to 9.5±2.5% at the most recent visit.

At the most recent visit, 3.5% (n=2/57) had neuropathy, 10.1% (n=10/99) had nephropathy and 18.2% (n=18/99) had microalbuminuria (MA). These rates, however, were not significantly different from those seen at the first visit (neuropathy 2.2%, n=5; nephropathy 5.3%, n=8; MA 18.5%, n=28, table 15). The prevalence of hypertension, however, increased significantly over time (39.0% to 46.6%). Similar results were seen for those who were tested at both time points (data not shown). At the most recent visit there were 8 new cases of MA, 7 new cases of nephropathy, 82 new cases of hypertension, and 1 new case of neuropathy. The estimates of annual incidence of complications were therefore, 6.4% (95% CI, 2.7-12.6) for MA, 5.6% (95% CI, 2.2-11.5) for nephropathy, 10.5% (95% CI, 8.4-13.1) for hypertension, and 1.4% (95% CI, 0.03-7.8) for neuropathy.

6.4.2 Vital Status

A total of 25 participants (n=15 (60.0%) females; n=10 (40.0%) males) were known to have died as of November 1, 2011. Thus, the known crude mortality for this cohort was 6.9% (25/361; 95% CI, 4.5 – 10.2%) or 13.9/1,000 person years of diabetes (95% CI 9.0-20.6/1,000). However, since an additional 8 participants died in 2012, a more accurate estimate of mortality is 9.1% (33/361; 95% CI 6.3-12.8) or 18.1/1,000 person years of diabetes. The actual mortality rate, however, could be significantly different since vital status was unknown for 134 (26.8%) participants. In a worst-case scenario (assuming all had died), the mortality rate could be as high as 32.1% (159/495; 95% CI 27.0-37.1%) or 40.2/1,000 (95% CI 32.0-49.9/1,000) person years of diabetes; the most optimistic (assuming all are alive) would be 5.0% (25/495; 95% CI 3.3-7.4) or 12.3/1,000 (95% CI 7.9-18.1/1,000) person years of diabetes.

For those who died as of Nov 1, 2011, cause of death was unknown for 16 (64.0%), with hypoglycemia being the most common known cause (n=4, 16.0%), and renal failure accounting for 2 (8.0%) deaths. Single deaths resulted from gastroenteritis, pneumonia, pulmonary embolism, rectal hemorrhage/hepatitis, and hyperglycemia. Unfortunately, none of the reported deaths had an official autopsy. There were no significant differences in sex, province, age, age at diagnosis, or diabetes duration for those with and without known causes of death (data not shown).

Mean age at time of death was 19.4±4.0 years (range 12-25 years), mean age at diagnosis for the deceased was 14.1±5.0 years (range 1-23 years) and mean diabetes duration was 4.5±3.5 years (range 0-11 years), which were not significantly different from those alive (data not shown). Twenty-two of the deceased (88.0%) recorded having no glucose meter at home versus 33% (n=99) of those who were seen in the last year ($p<0.0001$). Eleven of those who died had a

recorded HbA1c value (mean 9.8±2.0%; 83±22 mmol/mol), with a mean number of HbA1c measures of 2.1±2.0 per person. This was significantly fewer than those alive (p=0.002). On average, the deceased waited 7.6±5.9 months between readings, though this was not significantly different than those alive. There were no significant associations between Province and mortality, though the Western Province had the highest number of deaths (n=9).

Five-year survival for this cohort was 93.8% (85.1% worst-case scenario) and 10-year survival was 82.5% (66.2% worst-case scenario) (figure 6A). Survival curves were censored at 10 years, as less than 20% of the original cohort remained after this duration. Survival did not differ significantly by sex, province, year of first visit, year of diagnosis, year of birth, diagnosis before or after 15 years of age, or complication status (data not shown). However, those whose first visit was in 2009 had significantly higher mortality rates than all subsequent years combined (p=0.03) (figure 6B).

Results from Cox regression models are shown in table 16; only variables which were significant univariately were reported. Age at diagnosis, BMI, monitoring frequency, number of injections and weight at last clinic visit were univariately (all negatively except for age at diagnosis) related to survival, as was weight at baseline (table 16). In a multivariable model, each additional year in age at diabetes diagnosis resulted in a 15% higher mortality risk (HR 1.15, 95% CI 1.03-1.29) when also controlled for weight at baseline and monitoring frequency. With the same model, each additional unit of BMI, decreased the risk of death by 22% (HR 0.78, 95% CI 0.67-0.91), and each additional monitoring per week decreased risk by 7% (HR 0.93, 95% CI 0.86-0.99).

6.5 DISCUSSION

In this study of the Natural History of the first 500 participants registered in the IDF's LFAC program in Rwanda, we estimated the crude mortality to be 6.9% (or 13.9/1,000 person years of diabetes), and determined that mortality was directly associated with age at diabetes diagnosis, and inversely to year of first visit, weight at baseline, and monitoring frequency. However, since vital status is unknown for 134 participants, mortality could be as high as 32.1% (or 40.2/1,000 person years of diabetes). For the 310 with multiple visits, we saw a significant decrease in HbA1c (11.1±2.7% to 9.5±2.5%) and consistent rates of complications except for hypertension, which saw a significant increase. The majority of participants were returning within the recommended time frame of 3-6 months for clinic visits (57.5%) and HbA1c tests (59.7%).

Our estimated mortality and survival rates (5-year survival=93.8-85.1%; 10 year survival=82.5-66.2%) are consistent with previous studies from other youth cohorts with T1D in Africa (table 22). They are similar to those in Ethiopia (mortality=15.5/1,000 person years)[56] and South Africa (10-year survival=84%),[65] though survival in Tanzania was significantly poorer (5-year survival 71-60%).[42] Studies of mortality in youth with T1D from developed countries, however, reported much lower rates than Rwanda and ranged from 0.06% in the UK [150] to 6.1/1,000 person years of diabetes in Lithuania.[151–153] A 30-year mortality report from the US showed that African Americans with T1D had a mortality rate of 15.8/1,000 person years of diabetes,[87] which was higher than in Rwanda, but within our worst-case scenario range. Follow up time for several of these studies, however, was considerably longer than ours, so any direct comparisons would likely be limited.

Another mortality study that estimated life expectancy for newly diagnosed T1D patients in Mozambique and Zambia identified associations between life expectancy, location (urban vs rural) and diagnosis age.[89] The shortest life expectancy was seen in rural Mozambique, where those diagnosed before age 15 years had only a mean expectancy of 0.6 years. The longest life expectancy was seen in the urban capital city of Zambia, where life expectancy was on average 27.0 years. In Rwanda, however, we found no relationship between location and mortality. Although a somewhat higher percentage of those who died were from the Western province, the difference in survival was not significant. The observed higher rate in the West was not likely due to worse care, but rather to better reporting, as the local staff has been exceptionally consistent with regular follow-up and reporting.

While we found no difference in survival by diagnosis before or after 15 years of age, we did find differences with the continuous variable for age at diagnosis. Each additional year of age at diagnosis conferred a higher risk of mortality. Though this seems to contradict the results from Mozambique and Zambia (which reported longer life expectancy with older age at diagnosis), we believe that the increased risk of mortality in Rwanda with advanced age at diagnosis may partially be due to the effects of surviving for several years with undiagnosed diabetes. We hypothesize that by the time these participants are formally diagnosed, they are in especially poor condition and therefore at a higher risk of complications and death. Our findings that higher BMI and weight at baseline is protective, however, support this hypothesis, as we have previously found that those in worse control have lower weight consistent with lack of insulin and dehydration/hypovolemia.[118] Mortality data from T1D in Estonia, Lithuania, and Finland also found a similar association between age at diagnosis and mortality (14%), consistent with our findings.[151]

Though we have limited follow up data to document temporal improvements in survival, the data so far are encouraging, and suggest that as awareness of and care for diabetes increases, so does survival. This is consistent with the general improvement of life expectancy in T1D in developed countries.[154]

The majority of those who were deceased previously reported not having a meter at home. Having no meter makes it very hard to regulate diabetes control and greatly complicates the process of adjusting insulin properly. Thus, it is not unexpected that the main known cause of death was hypoglycemia. This finding is also consistent with many others that indicate that within the first 10 years, cause of death is primarily due to acute causes.[87] Sixteen percent of deaths (n=4) in our cohort were due to hypoglycemia, which is considerably higher than rates seen in Dar es Salaam (5%; n=2 with 5 years follow up)[58] and Ethiopia (7.1% with 15 years duration). [56] These results underscore the importance of ensuring that all LFAC members have access to glucose meters and strips and appropriate education, especially in light of the high rate of food insecurity in this population. It is, however, very likely that several of the deaths due to unknown causes were from DKA, but were not properly identified as such. Therefore, we cannot say that hypoglycemia is the most common cause of death, as over half were due to unknown causes.

Although 18.8% of our initial cohort has been lost to follow up, similar results were reported from the other mortality studies in Africa. In Tanzania 11% of the cohort had not been heard from for 3+ years[58] while even higher percentages were lost to follow-up in Ethiopia (33.4%)[56] and Soweto (27.3%).[65,155] They each reported difficulties due to a country-wide lack of official home addresses, incorrect contact information, and movement from the area, which were also major barriers in our study. The most frequently provided reasons for non-attendance in

Rwanda were: being away at school, lack of transport, and no knowledge of the visit dates. Radio announcements have been the preferred method of announcing clinic visit dates, but this requires that the participants have access to a radio. Unfortunately at this time, we are unable to provide services through schools, but are working on developing awareness programs within schools, working with local nurses to help provide for transport, and developing local support groups of children that provide phone chains and social incentives to attend visits. It is also unclear at this time as to whether children are receiving care elsewhere between visits. However, due to the lack of insulin and high prices of diabetes care, we believe this is unlikely.

The high turnover rate of the nursing (and medical) staff at the district hospitals has also limited our follow up of LFAC participants, and many of the new nurses have never seen the patients we are trying to locate. The support groups have worked towards limiting the impact of the nurse turnover, and even in locations where the nursing staff has been stable, the children are usually the best source of information on missing members.

Over the course of the LFAC program, several individuals have come back to the clinic years after their last insulin dose (n=21 after 2 years; n=2 after 3 years). This phenomenon has also been recorded in children with T1D in Ethiopia who had interrupted insulin supplies (for 9±12 weeks; range 1-78 weeks), of whom only 4% developed any DKA. [156] While these individuals were in poor condition when they returned, the fact that they survived so long without any exogenous insulin suggests that there may be a different type of diabetes (with some significant residual beta cell function) present in this population. This would be consistent with results from other studies from Ethiopia, suggesting the previously recognized "Malnutrition-related Diabetes" (MRDM) should be re-considered in Africa.[47,157,158]

The prevalence of neuropathy in our cohort (3.6%) was lower than those in other African countries (Addis Ababa, Ethiopia =7.9%;[56] and Soweto, South Africa =35.3%).[65] Also, the prevalence of microalbuminuria (18.2%) was lower than in Soweto, South Africa (26.3%; mean duration 13.6 years; Dipstick test)[155] and Tanzania (29.3%; mean age of 21 years and duration of 3 years; MICROTEX).[76] The annual incidence of MA was significantly higher than that from Denmark (1.9%; 12.2 years duration)[129] and other developed countries (Australia 4.6/1,000 person years; 6.7 years duration).[130] A direct comparison of complication rates is limited due to the differing means of assessment. However, as duration of diabetes was significantly shorter in our population than the other African studies, this raises concern that the rates of microalbuminuria in our population are indeed higher.

The prevalence of hypertension increased over time and was also elevated in this population in comparison to rates reported in US African Americans (AfAm=9.8%, Rwanda 46.6%).[11] We have previously postulated that this is due to the poorer glucose control in Rwanda, as those whose control worsened overtime saw more dramatic increases in BP over time than those who were in good control or who saw improved control (Marshall, Paper 1). However, BP was still higher in those who saw improvements in glucose control than those who had constant tight control, suggesting a residual effect. Additional studies from sub-Saharan Africa have shown that rates of hypertension for those under age 45 are higher than the US and the UK (SSA=10.7%, UK=5.6%, US=8.2%), and that it may be due to excess salt in food preparation.[136] This increase in hypertension prevalence, and the positive association between hypertension and microalbuminuria, highlights the need for improved BP control in this cohort for complication and mortality prevention.

The key limitation for this study was our use of routinely collected clinic data instead of study data. This meant we were restricted to the data collected on the LFAC forms and had to rely on unconfirmed dates of birth, diagnosis and death, as well as self-reported data for monitoring frequency and insulin dosage. Complication assessment was also limited due to logistical issues (eg. microalbuminuria testing supplies). Mortality data was also limited due to lack of autopsy data and a formal national death index. This, therefore, led to the wide range of possible mortality rates and highlights the importance of establishing better follow up protocols for the future.

The major strengths of this study are that our cohort consists of 500 participants, which is the largest cohort for which mortality of T1D in sub-Saharan Africa has been reported. In addition we have compiled a large amount of temporal data that spans eight years (2004-2012). This is also the first follow-up and mortality report for diabetic youth and adolescents in Rwanda.

In summary, these data demonstrate that mortality rates for those with T1D in Rwanda are similar to other African T1D populations, but higher than those in developed countries. Delayed diagnosis of T1D may be driving the increased risk seen in those diagnosed at an older age, thus highlighting the importance for increased awareness and timely diagnosis. However, the improvements in survival since 2009 are encouraging. Utilization of the LFAC program in Rwanda has increased significantly since its inception in 2004, and HbA1c has decreased considerably as a cumulative result of its efforts. Hypertension, however, remains an issue in this population and is increasing overtime. This needs to be further investigated and addressed appropriately. Although several of our participants have died and more have been lost to follow-

up, we hope that by recognizing and addressing the identified barriers, more thorough and timely care will be available in the future.

6.6 TABLES

Table 14. Characteristics of participants with multiple clinic visits from 2009-2012, those who only had one clinic visit, and those who have no recorded clinic visits.

	Visit Status		
	Multiple-visits	One Visit	No visit[$]
N	370	53	65
Age at Diagnosis (years)	15.4±4.9	16.8±5.1	12.7±5.8*
Male (column% (n))	43.0 (156)	43.4 (23)	44.6 (29)
Age in 2012 (years)	20.8±4.6	22.3±5.0	20.7±4.9
Province (row% (n))			
East	73.1 (38)	7.7 (4)	19.2 (10)
Kigali City	71.5 (88)	9.7 (12)	18.7 (23)
North	84.2 (48)	8.8 (5)	7.0 (4)
West	76.2 (64)	15.5 (13)	8.3 (7)
South	72.2 (130)	10.6 (19)	17.2 (31)
Year of First Visit % (n)			
2009	159 (87.4)	23 (12.6)	-
2010	126 (87.5)	18 (12.5)	-
2011	82 (88.2)	11 (11.8)	-
2012	3 (75.0)	1 (25.0)	-

* Significantly different from those with multi-visits and one visit

[$] Excludes an additional 12 with no visit, but with no demographic or clinical data reported

Table 15. Clinic data from the first and most recent clinic visit for participants who had multiple visits between 2008-2012.

	First Clinic Visit	Most Recent Clinic Visit
Time Between Visits (months)		26.6±10.8
Age (years)	18.6±4.5	20.6±4.5*
Male %(n)	43.0 (156)	
Age at Diagnosis (years)	15.4±4.9	
Duration of diabetes (years)	3.0±2.9	5.0±3.1*
Glucose Monitoring (per week)	1.3±3.9	8.0±8.0*
HbA1c (mmol/mol)	98±30	80±28*
HbA1c (%)	11.1±2.7	9.5±2.5*
<8.0%	17.0 (55)	28.9 (96)*
8-11.9%	40.9 (132)	51.5 (171)*
12-14%	14.6 (47)	9.6 (32)*
>14%	27.6 (89)	9.6 (32)*
Insulin Injections (per day)	1.8±0.6	2.0±0.5*
Units of Insulin (per day)	32.4±15.7	37.8±15.4*
Units of insulin per kilogram	0.70±0.37	0.75±0.30
Weight (kg)	47.6±12.6	51.6±11.6*
Height (cm)	154.5±14.3	156.7±12.8*
BMI (kg/m^2)	19.8±3.5	20.7±3.2*
Systolic BP (mmHg)	113±16	120±17*
Diastolic BP (mmHg)	73±12	79±12*
Neuropathy %(n)	2.2 (5) [a]	3.5 (2) [b]
Microalbuminuria %(n)	18.5 (28) [c]	18.2 (18) [d]
Nephropathy %(n)	5.3 (8)[c]	10.1 (10)[d]
Hypertension %(n)	39.0 (141)[f]	46.6 (167)[g]*

* Significantly different from first clinic visit ($p<0.05$)

[a] n tested=230
[b] n tested=57
[c] n tested=151
[d] n tested=99
[f] n tested=362
[g] n tested=358

Table 16. Cox regression models for mortality. HRs and their associated 95% CIs are reported.

	Variables that were univariately significant		**Model I**	
	HR (95% CI)	**p**	**HR (95% CI)**	**P**
Age at Diagnosis (years)	1.12 (1.01-1.2)	0.01	1.15 (1.03-1.29)	0.01
BMI at most recent visit	0.80 (0.70-0.92)	0.002	0.78 (0.67-0.91)	0.001
Monitoring Frequency at most recent visit (times per week)	0.91 (0.85-0.97)	0.006	0.93 (0.86-0.99)	0.046
Number of injections at most recent visit (per day)	0.50 (0.26-0.98)	0.03	N/S	-
Weight at baseline (kg)	0.96 (0.93-0.99)	0.02	N/S	-
Weight at most recent visit (kg)	0.94 (0.91-0.97)	0.002	N/S	-

6.7 FIGURES

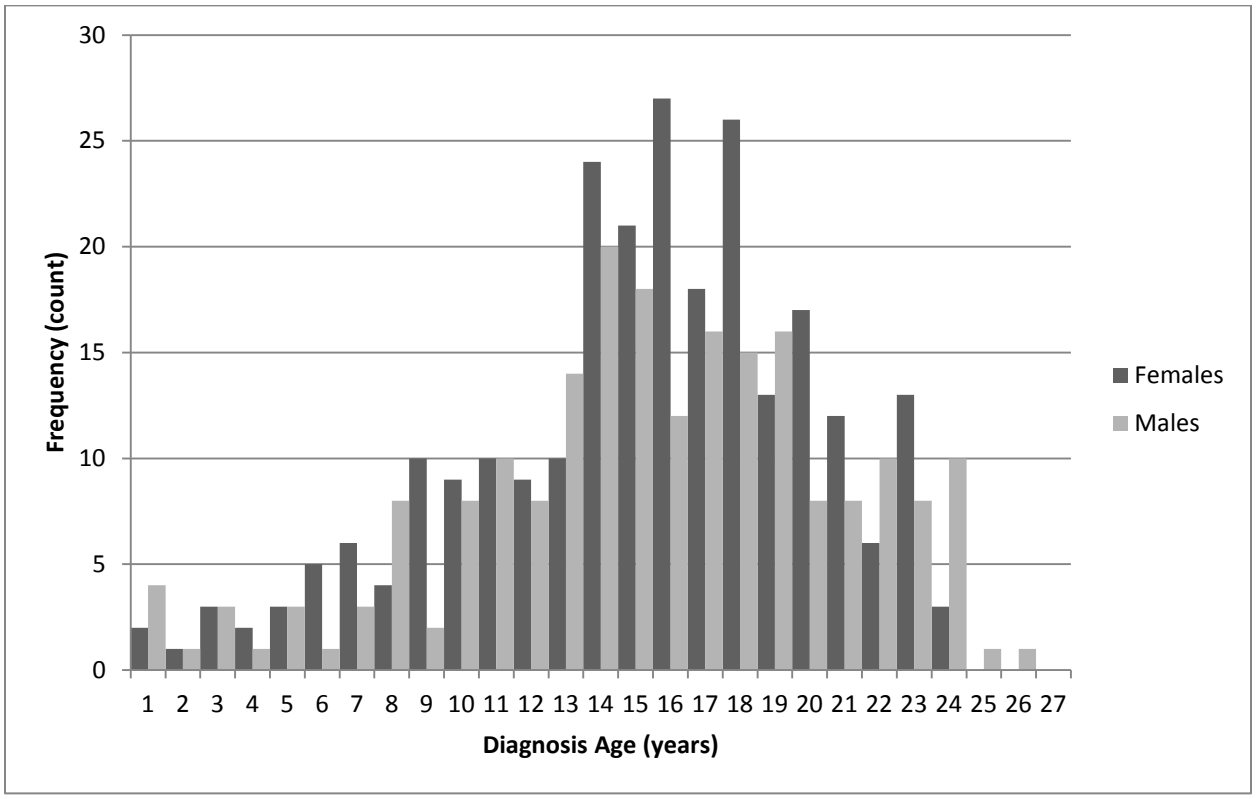


Figure 4. Histogram of diagnosis age for the first 500 LFAC program participants, by sex.

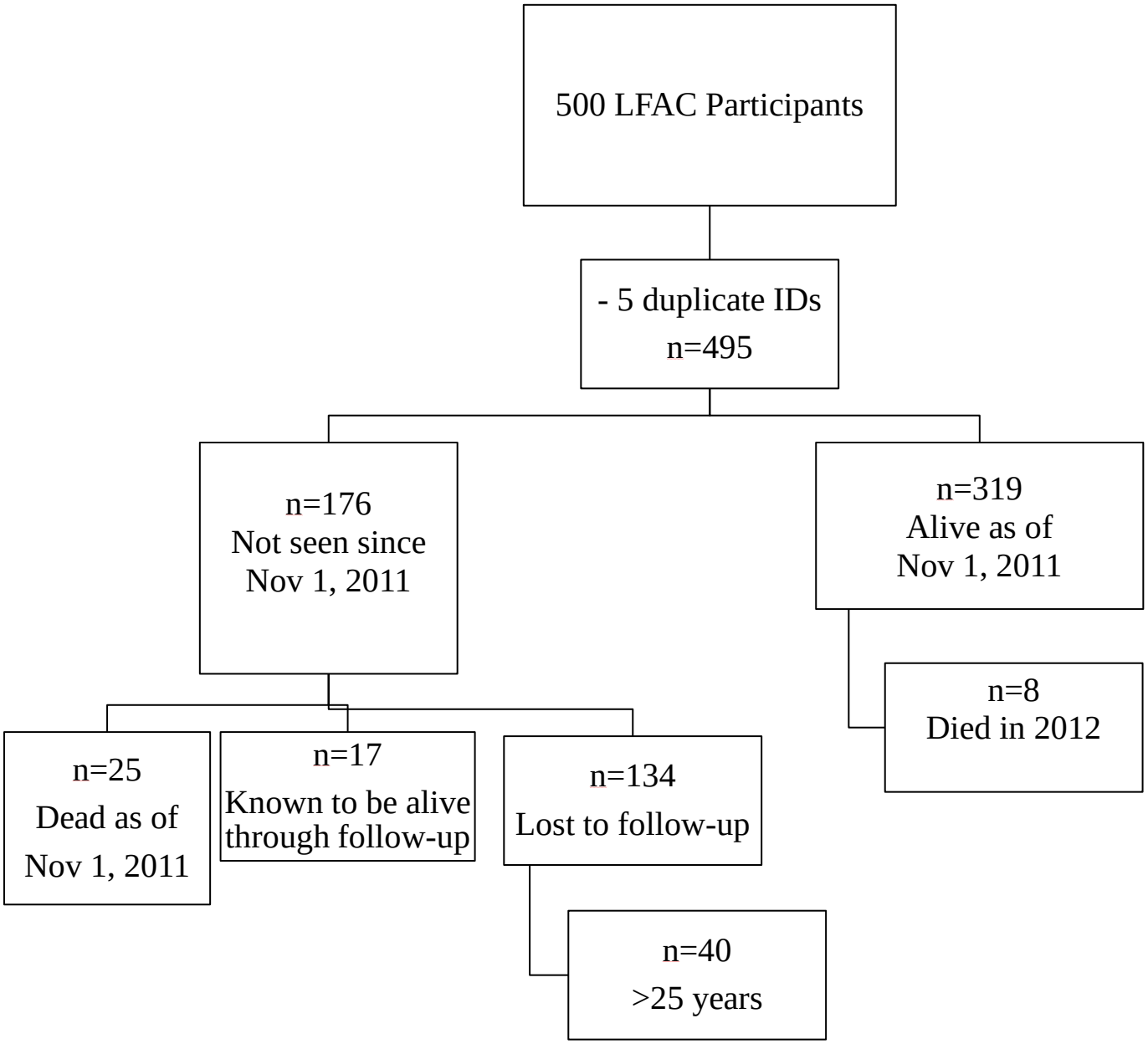


Figure 5. Flow chart outlining participant follow-up and vital status.

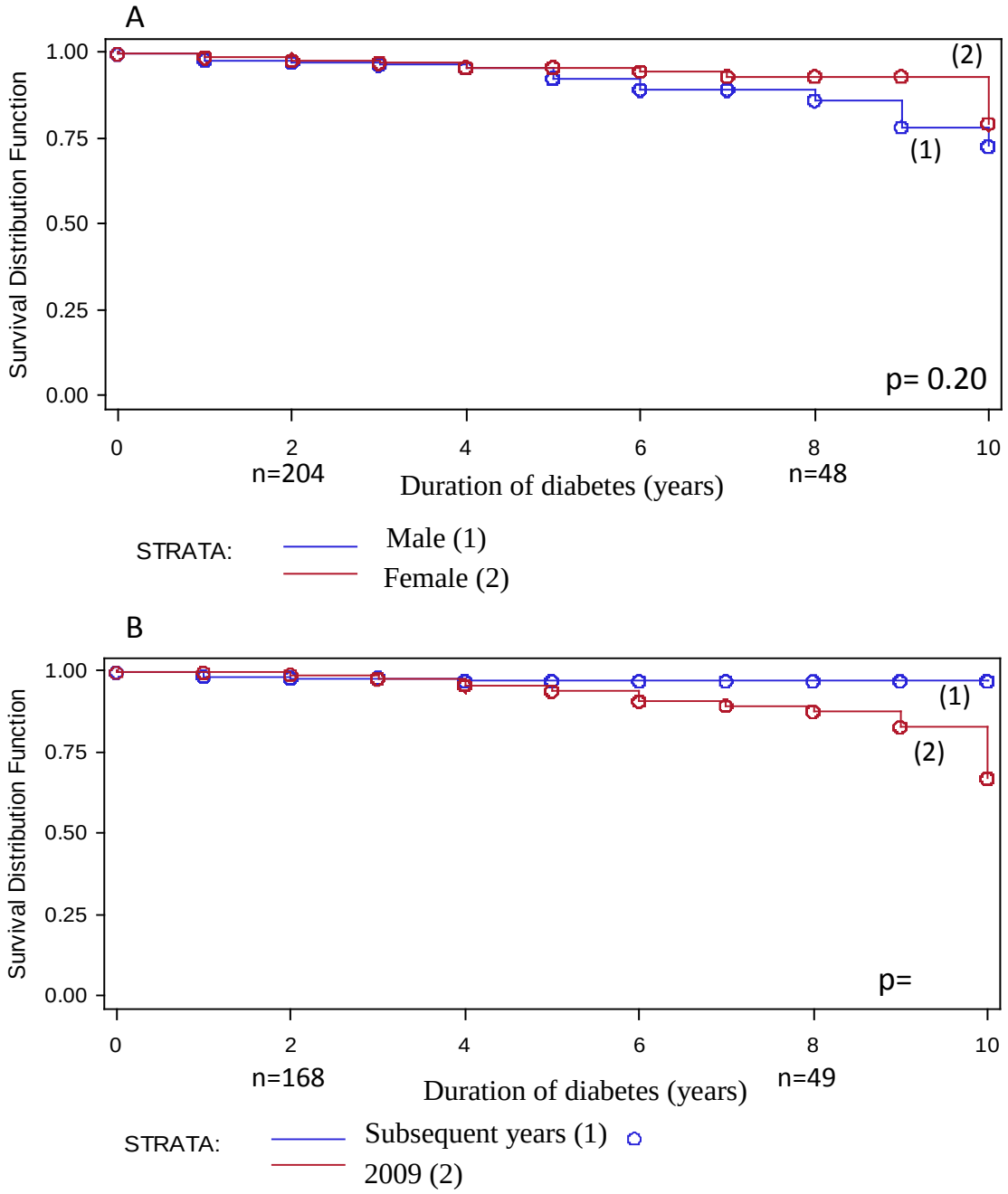


Figure 6. Survival by Sex (A) and Year of First Clinic visit (2009 vs all subsequent years) (B).

7.0 DISCUSSION

7.1 SUMMARY AND CONCLUSIONS

These data represent the first attempt to describe the magnitude (incidence/prevalence) and natural history of type 1 diabetes (T1D) in Rwandan youth. This dissertation also assesses the impacts of the Life For a Child program on this growing issue in this economically challenged country. Though we were unable to undertake a true epidemiological study with screening for of the incident and prevalent cases of T1D in Rwanda, our data still suggest that the rates in Rwanda are relatively low as compared to other sub-Saharan African countries[31] and African-Arabic countries.[22,23,26,29,30,32] Incidence of recognized T1D has, however, increased 4-fold over the last several years, portending a larger Public Health issue in the near future. We now know that additional efforts are needed to ensure proper and timely diagnosis, as it appears very likely that many cases are dying before diagnosis, or are being misdiagnosed, especially in those less than 5 years of age.

This study was the first to describe the natural history of T1D in Rwanda and identified hypoglycemia as a major cause of death. While the mortality rate in Rwanda was similar to several other African countries [Ethiopia[56], Tanzania[58], South Africa[155]], it was significantly higher than rates seen in developed countries.[87,150–153] Rates of complications, specifically hypertension and microalbuminuria, were higher in Rwanda than other African T1D youth cohorts[56,65,76] and suggested an earlier development of complications. These findings raise concerns for the future health of this population.

In the face of these negative outcomes, we did, however, demonstrate that glycemic control could be improved in a country with limited resources, and confirmed increased glucose monitoring as a potential intervention point. Application of trajectory analysis to our data allowed us to identify glycemic control sub-groups and future use of this technique could lead to more targeted interventions based on current control.

Though these results are promising, it is clear that further research and interventions are still needed to adequately address T1D in Rwanda. Additional efforts are needed to address the issues of balancing glycemic control and fear of hypoglycemia, especially in this population where food insecurity is common. Outreach to other regional hospitals and education for patients, their caregivers and other community members needs to be improved to ensure this disease is properly addressed. We must also take steps to further improve prevention, diagnosis, and treatment of complications of T1D. Finally, additional strides need to be taken towards making this program more sustainable long-term, so that proper care may be available well into the future.

7.2 GENERAL FINDINGS

7.2.1 Context of Data Collection

The Life For a Child (LFAC) program in Rwanda started in 2004 at the Association Rwandaise des Diabetiques (ARD) with only 25 children. While the program focused on providing support to allow for the best possible clinical management for children with T1D, an important early goal was ensuring that every district hospital had access to a glucometer. Prior to this initiative, almost no hospitals in Rwanda had access to meters, thus severely limiting their ability to diagnose diabetes. Parallel to this movement, the World Diabetes Foundation provided monetary

support for education sessions for doctors and nurses on how to properly recognize diabetes cases as well as provide proper management. Since doctors in Rwanda reportedly receive less than 32 hours of training on the endocrine system as a whole, yielding very little time to address diabetes, these training sessions were critically needed.

In 2007, Dr. Trevor Orchard, from the University of Pittsburgh's Graduate School of Public Health (GSPH), voluntarily became involved with the Rwanda LFAC program. This program is primarily focused on assisting local health care providers - particularly diabetes associations - provide insulin, diabetes care and education to youth with diabetes. Dr. Orchard's, and therefore GSPH's, involvement was thus concentrated first and foremost on addressing the urgent humanitarian needs of the diabetic youth and the public health concerns, with research being only a secondary aim. Early in this process Dr. Orchard worked early with Dr. Graham Ogle (the LFAC General Manager) in revising and standardizing the LFAC data collection protocol and forms. After an initial assessment of the diabetes care available in Rwanda (2008) – taking into account the current lack of knowledge, awareness, and treatment options of diabetes - Dr. Orchard made the executive decision to build on the current system of collecting clinical data for the LFAC program, and to not complicate the situation and divert resources from the humanitarian need by collecting any research data. This approach also concentrated the limited resources on care and education.

Though this decision allowed for a smooth transition and a continuation of aid and routinely collected data, that did not require consenting, it also negated the benefit afforded by "formal" research which collects high quality data. Thus, dates (birth, diagnosis, and death) are not fully confirmed as is also true for self-reported data for monitoring and treatment. Indeed, on the initial 2008 assessment, it was found that while the ARD did a heroic job in the face of little

resources, basic concepts of patient care (eg. maintaining individual patient charts) were not in operation. The on-going nature of this project evaluation, in combination with incomplete data due to loss to follow-up, means that no single true intervention could be examined, as improvements in care and education were staggered as resources permitted, and clinic data for some participants was scarce, if available at all.

Thus, the data available for this doctoral thesis, much of which I personally collected during seven visits to Rwanda, is limited to the routine clinical data available in a very impoverished country (Rwanda's GDP (nominal) is ranked number 141 out of 190 by the World Bank, and 44.9% live in poverty; average life expectancy=58.8 years)[114,141] with limited resources where such basic records as birth and death certificates are not routinely available, indeed many individuals do not know even their birth date. The impacts of the 1994 genocide are also still felt, as several participants are orphans and are left to care for themselves and sometimes for their siblings. This places an additional stress on the patient, and often results in extreme poverty.

Though the decision to use clinic data rather than study data had its drawbacks, it allowed us to focus primarily on providing care to participants and afforded us a large amount of data for a large cohort of T1D patients, which may not have been possible with a formal research project. The major weaknesses we saw in our data (uncertainty about dates, limited mortality data, self-reported data) would still have been present if we had undertaken a formal research study, as there exist no records of these dates and no formal way of eliminating self-report of some data points. Therefore, we believe the chosen path provided us with the best possible and most generalizable dataset for this population, while allowing us to focus on care and keep costs low.

That being said, the LFAC program has since expanded in scope, quality, and magnitude. As of December 2012, the LFAC registry included 820 children and adolescents from over 26 district hospitals. Although several have already aged out from the official program, many remain in contact with the ARD staff for management advice. Data collection frequency has increased from annually to quarterly, and official protocols for data collection and reporting have been adopted. Tests for glycemic control (HbA1c) and proteinuria (albumin/creatinine ratio; A/C ratio) are now available, and efforts to introduce retinopathy screenings are underway. Education sessions are now regularly held for both caregivers and patients, and support groups are being formed.

This partnership among the LFAC, the ARD, and GSPH, has resulted in over five years of directed diabetes management and data collection – data which we were then able to use to describe the current magnitude and burden of T1D in Rwandan children and adolescents, and to document improvements in glycemic control. This report, though limited in several aspects, is the first report on these items, and has the potential to impact future diabetes care in Rwanda as well as other developing countries.

7.2.2 Variations in T1D incidence/prevalence

Global variations in rates of T1D have been previously described and may span a 350-fold difference.[14,15] Even within Africa, prevalence and incidence rates of childhood T1D have ranged from a reported prevalence rate of 27/100,000 in Algeria[30] to 95/100,000 in Sudan[23] and an incidence of 1.5/100,000 in Tanzania[31] to 10.1/100,000 in Sudan.[22]

Our study found that the prevalence of clinically recognized T1D in Rwanda was significantly lower than previous reports from Africa[23,29,30] and was less than a tenth of those for

African Americans.[11] The incidence rate of T1D was lower in Rwanda than the highly Arabic countries of Sudan, Tunisia, Libya and Algeria[22,26,30,32], but was similar to those in Tanzania[31], highlighting potential ethnic variations in rates of T1D.

In Rwanda, we also noted a 4-fold increase in the incidence over the last 7 years, with stabilization within the last 5 years. Temporal trends in incidence of T1D have been previously noted. The global incidence of T1D is estimated to rise 3.0% annually.[15] In Africa, incidence rates also increased over time in Sudan,[22] Libya,[32] and Algeria,[30] but no changes were seen in Tunisia[26] or Tanzania.[31] Due to the potential for missed cases (under-diagnosis, death before diagnosis, or misdiagnosis) and the recent increased awareness of diabetes in Rwanda, it is impossible to determine if this is a true increase or an artifact, especially with the recent stabilization. It is of additional interest that during this time period, though overall incidence has stabilized, we have noticed a possible time*gender interaction as incidence for males has decreased and increased for females. Though this was not significant, it warrants further follow up.

Our report from Rwanda showed an overall higher prevalence in females (18.5/100,000) than males (14.1/100,000), and a similar pattern in incidence rate (females=3.4/100,000; males=1.5/100,000). On the whole, there are no significant global sex differences in incidence or prevalence of T1D.[14,15] However, several studies from Africa have shown these rates differ by sex. Sex differences in prevalence were seen in Sudan (females higher than males) and Nigeria (males higher than females),[23,29] but not in Algeria,[30] while a difference in incidence by sex was seen in Libya (females higher than males).[32] While the gender results from Rwanda were different than the overall global results and several countries in Africa, they were similar to some data from the US. In the US, no sex differences have been seen for the overall population,[159] but

for African Americans aged 10-14 years, the incidence (females=26.1/100,000; males=16.7/100,000) and prevalence (females=210/100,000; males=150/100,000) of T1D was higher in females than males.[11] Furthermore, previous studies in the US Virgin Islands and the US, non-hispanic blacks have not seen a pubertal rise in incidence for males in blacks.[11,160] While we did not note this pubertal sex difference, it is clear that the excess female cases in Rwanda is primarily due to the higher rate of females diagnosed between the ages of 14-18 years, which might reflect a similar phenomenon.

There was a notable positive age trend in rates in Rwanda. Prevalence ranged from 0.6/100,000 for those 1-4 years, to 54.1/100,000 for those aged 20-24 years, and incidence in 2011 increased from 0.0/100,000 for ages 1-4 years to 5.2/100,000 for those 20-24 years. Global age trends in rates have been reported.[15] Incidence rates by age group are significantly different for most countries, with incidence increasing with age. In the US, the highest incidence rates of T1D were seen in those aged 10-14 years (25.9/100,000),[12] and prevalence was higher for those aged 10-19 years (228/100,000) than those 0-9 years (76/100,000).[159] Similar patterns by age were seen for prevalence of T1D in African American youth (0-9 years=57/100,000; 10-19 years = 204/100,000), though no significant differences were found for incidence.[11] Similar patterns were seen in Africa, where prevalence increased with age in Sudan and Nigeria,[23,29] and incidence increased with age in Tunisia and Tanzania.[26,31]

There are several theories as to what is causing this global variation in incidence and prevalence of T1D. One theory is based on unreliable case ascertainment. The thought is that early reports missed cases either due to under-diagnosis or misdiagnosis, and that as time has passed, awareness of T1D has improved and thus diagnosis and reporting have improved as well. We believe this may be a possible reason for the previously low rate of recorded cases under the

age of 5 years in Rwanda, and the recent increases in prevalence and incidence. However, the majority (>80%) of the studies used for global comparisons make use of the capture-recapture method, and therefore the impacts of this upon their noted global variation were likely limited.[15] Unfortunately, due to the short time period of data collection that was covered in the global comparisons (~5 years), it is impossible to tease out the impacts of data collection/under-ascertainment from other possible causes of variation.

Differences in T1D incidence/prevalence rates have also been ascribed to genes, environment, viral infections, dietary exposures, behavioral stressors, changes in hygiene, and exposure to childhood infections.[7,144–146,161,162] Since these increases in incidence of T1D have been seen over such short time periods (~5-10 years) it is highly unlikely that the changes can be completely due to genetic shifts in susceptibility, thus suggesting that further work be done to examine environmental impacts or gene-environment interactions. Changes in BMI have also been implicated, as an association between early obesity and increased T1D has been seen,[163] though it is unlikely that this is a driving factor in Rwanda, as no significant changes in BMI have been seen and less than 10% of our cohort was overweight or obese. Psychological stress has also been linked to diabetes-associated auto-antibodies in children.[164] While this may not be especially relevant globally, it could be an issue of interest in Rwanda, considering the on-going regional political unrest and the lingering impacts of the 1994 genocide.

Early exposure to cow's milk may be another potentially important factor to consider when comparing rates of T1D in Rwanda to other countries. In previous reports, rates of exclusive breastfeeding were higher in Rwanda[147] (91.4% for 0-1 months to 75.7% for 4-5 months) than Nigeria[148] (2.1% for 0-1 months to 0.1% for 4-5 months) and Tanzania[149] (55.2% for 0-1 months to 8.0% for 4-5 months). This lower rate of early exposure to cow's milk may

contribute to the lower risk of developing T1D in Rwanda than the other African countries. Genetics may also play a role in the lower rates in Rwanda, as the previous African studies were in primarily Arab countries, which have been shown to have very high rates of diabetes.[2,14] As the majority of the Rwandan people are not of Arab descent, the rate of T1D might therefore be expected to be lower in Rwanda than the previous studies. This idea is supported by the fact that the rates seen in Rwanda were most similar to those in Tanzania, which has a more similar genetic profile.

Due to this uncertainty surrounding the cause of the geographic variations of T1D and the evolution of diagnostic criteria, it is necessary to continue to monitor the rates of T1D. As we work to determine the etiology of this disease as well as the determinants of variation due to time, age, sex and race, it may behoove researchers to study the impacts of social events as well as genetic and environmental factors.

7.2.3 Managing Diabetes in Africa

In light of these increasing rates of T1D, resource poor countries will have to make major adjustments in their healthcare systems to be able to properly diagnose and manage patients with T1D. Seeing as prior to 2004, hospitals in Rwanda did not have access to glucometers and that only 18% and 8% of healthcare centers in Mozambique had access to glucometers and ketone tests, respectively, diagnostic procedures will need to be addressed first.[89] However, once a patient has been diagnosed with T1D, access to insulin becomes another issue. 50-70% of T1D patients in the Congo, DRC, Cote d'Ivoire, Madagascar and Togo, 25-49% of those in Mali and Uganda, and 1-24% of patients in Nigeria and Senegal were unable to access insulin because it was too expensive, was not available, or had issues with storage.[103] We saw the same barriers to

care in Rwanda, as insulin was primarily unobtainable outside our program due to low availability and prohibitively high prices. The same issues were true for the remaining management supplies (meters, strips, and syringes).

The LFAC has worked to address these barriers to care in developing countries, through provision of education materials, insulin and diabetes management supplies. In order to continue their efforts globally, they need to ensure that their resources are being properly used to manage diabetes appropriately. One way to achieve this is through twinning of newer diabetes centers in developing countries with well-established programs in developed countries, such as the agreements between the Diabetes UK with Mozambique Diabetes Association[111] and the National Diabetes Program in Tanzania.[112] Our partnership with the ARD was initiated with the same goals in mind – to provide advice and direct assistance to the ARD staff, and maximize the proper use and allocation of resources supplied by the LFAC program.

In order to assess the effectiveness of the LFAC program in Rwanda, we used HbA1c testing as a marker of glycemic control. At baseline, mean HbA1c was 11.2±2.7% and 30.8% of the cohort had very poor glycemic control (HbA1c >14%). However, as the LFAC program evolved through the addition of education sessions, more frequent clinic visits and regular HbA1c monitoring, mean HbA1c fell to 10.2±2.6% 12-months after baseline and to 9.8±2.3% 24-months after baseline. The proportion of those with HbA1c over 14% also fell to 12.2% at 12 months and 9.0% at 24 months. We also identified more frequent glucose monitoring as a potential point of intervention for improving glycemic control. This finding confirms the need for consistent availability of glucose meters and strips for proper management of T1D, as well as the need for knowledge of how to properly adjust insulin regimens based on glucose monitoring results.

The improvements we have seen in HbA1c control in Rwanda have resulted in a lower cumulative glycemic exposure. In order to estimate this exposure, a variable named A1months was developed that accounted for both magnitude and duration of exposure. This variable is calculated by summing the number of months from diagnosis to the current reading X the HbA1c units above the normal.[165] For the cohort we followed, those who attended all three visits saw a total reduction in A1months of 3,363 months, with an average of 26.9 months per person (range 0-122.4 months). This decrease in glycemic exposure will likely result in delayed development of complications and reduced mortality.[165–168]

Though these initial improvements in Rwanda are encouraging, it is apparent that additional work still needs to be done. While mean HbA1c has decreased since 2009, there are still patients who have un-measureable (>14% HbA1c) glycemic control, and a number of participants still have HbA1c's that are well above the recommended goals of 8.5% for those younger than 6 years, <8.0% for those 6-13 years and <7.5% for those over 13 years.[5] Hopefully in the future, these patients can be identified and be provided targeted care, specific to their situation and home life. That being said, the efforts and improvements that have been seen are commendable considering the lack of resources and low education and organization of the general healthcare system in Rwanda. It is very likely that without the LFAC, ARD and GSPH intervention the status of the majority of these patients would be definitively worse.

A previous study from Kenya showed improvements in glucose control with increases in glucose monitoring and regular contact with diabetes caregivers.[126] Additional studies from Eritrea and South Africa have shown that a combination of education programs and HbA1c testing can result in improved glycemic control.[108,110] However, these studies were done in significantly older populations and were primarily for those with type 2 diabetes. Therefore, our

study appears to be the first documentation of improved glycemic control in children and adolescents with type 1 diabetes in sub-Saharan Africa. Our results show that despite the previously identified barriers, glycemic control can be obtained with outside support from organizations such as the LFAC program.

Though programs like LFAC may assist in providing supplies for the management of diabetes, the hospitals will also have to make adjustments in their approach, as they will have to provide long-term treatment instead of the usual short-term treatment for communicable diseases. Hospitals will have to improve upon their current record systems to allow for easy and effective patient follow-up.

7.2.4 Complications of T1D in children and adolescents

Though we've seen improvements in glycemic control in Rwanda, complications due to diabetes are still present, or in the case of hypertension, are on the rise.

Our reports show that the rates for microalbuminuria (MA), nephropathy, and neuropathy in Rwanda have not increased significantly over the last several years. Unfortunately, due to differing definitions and means of assessment, direct comparison of rates of complications is difficult. Duration is a well-established risk factor for microalbuminuria[131,132,169] while neuropathy,[170] and poor metabolic control are also associated with increased risk of complication development.[60] Similar associations were found in our analyses as well.

In Rwanda, we saw rates of neuropathy that ranged from 0.0% - 3.6%, which is lower than those reported from Ethiopia and South Africa (10.4% and 35.3%, respectively).[56,109] Unfortunately, comparison to other studies is complicated as the reported rates of T1D peripheral

neuropathy range from 7-57%, with the wide range due to different diagnostic methods and criteria.[171]

While the prevalence of MA did not change overtime, it was more commonly seen than nephropathy (MA=18.2-21.0%). Table 17 compares rates of MA for Rwanda and other youth and adolescent T1D populations, as well as mean diabetes duration and mean HbA1c (or % of population with HbA1c <8%).[56,57,129,133,155,172,173]. Though each of these studies was performed in similar ages, duration of diabetes, glycemic control (HbA1c) and MA rates were quite different.

Table 17. Comparison of rates of microalbuminuria, duration of diabetes and HbA1c by country.

Country	Duration (years)	HbA1c (%)	% with HbA1c <8%	Testing Method	Microalbuminura (% n)
Rwanda	5.0	11.2±2.7	-	A/C ratio 30-299 mg/g	18.2-21
Tanzania	4.76	10.65±2.1	-	MICROTEX (albumin >2.5 mg/dl)	29.3
South Africa	13.6	-	-	Dipstick albumin >30 mg/L	26.3
Australia	6.8	8.5±0.7	-	AER ≥20-150 µg/min	6.0
Denmark	12.2	9.7±1.7	-	AER ≥20-150 µg/min	9.0
US Overall (0-17 years)	3.7	-	~30%	A/C ratio ≥30mg/g	9.2*
US Af Americans (0-17 years)	3.7	-	~30%	A/C ratio ≥30mg/g	9.6*
Rwanda Youth (0-17 years)	3.8	-	18.9%	A/C ratio ≥30mg/g	13.3*
Pittsburgh (6-21 years)	5.0	11.8±1.4	-	AER ≥20-150 µg/min	21.0
Rwanda (6-21 years)	5.0	10.1±2.4	-	A/C ratio 30-299 mg/g	15.1

*Rates of all elevated A/C levels (ACR) (both MA and nephropathy combined) are presented

Based on the known relationship between both MA and neuropathy with duration, one would therefore expect the prevalence of MA and neuropathy in Rwanda to be lower than all the

previous studies with the exception of Tanzania. However, while rates of neuropathy were lower than previous studies, the rates of MA in Rwanda are actually higher than all but Tanzania. One potential cause of this unexpected relationship with MA may be due to the other predictor of MA – glycemic control. Our Rwanda cohort had very poor glycemic control at baseline with a mean HbA1c significantly higher than those seen in developed countries, but comparable to those in Africa. The higher HbA1c could therefore account for some of the difference in prevalence of MA, and supports our findings of rates that are closer to those seen in other African countries.

The differences in diabetes duration and glycemic control likely do not, however, account for all of the additional risk seen in Rwanda. One other factor that may be contributing to this excess risk is hypertension. The true association between hypertension and MA has still not been determined, as hypertension has been reported as both a causative factor for and a result of MA.[132,174,175] In Rwanda, however, we have reported increases in risk of MA with increases in blood pressure,[118] which this is supported by other work in Africa,[176] and developed countries.[170,172,173] This is an especially important relationship to be aware of in our Rwanda population, as rates of hypertension (28.5-45.3%) are high in comparison to other T1D populations (Australia=16.0%,[172] US overall=5.9%, US AfAm= 7.8%,[134] Pittsburgh, USA[133];% sbp $\geq$120 mmHg =11.9%; Rwanda=28.6%; % dbp $\geq$80 mmHg Pittsburgh=10.2%, Rwanda=42.8%) and rates of MA are already elevated.

The reason for the elevated hypertension in this population is likely due in part to the poor glycemic control. In Rwanda, while there were no overall significant differences by HbA1c control groups, BP increased the most for Group 2 (low-increased) and the least for Group 1 (low-low), while BP for Group 3 (intermediate-low) did not change significantly. Although BP also increased for Group 4 (high-declined), it was likely as a result of improved health, as

previously described for this cohort,[118] since weight also increased as HbA1c decreased. Previous studies have also found an association between poor glycemic control and higher rates of hypertension.[134,177,178] Additionally, prior studies found that in the general population the prevalence of hypertension in those under age 45 years was higher sub-Saharan Africa (SSA) than the US and the UK (SSA=10.7%, UK=5.6%, US=8.2%).[136] Diet may contribute to this additional risk, as salt is often used to prepare and preserve foods in SSA. Unfortunately we had no dietary information for this cohort, so we were unable to determine the actual salt intake for those in the LFAC program.

If hypertension is not addressed in this population, it is very likely that the overall rates of long-term complications will rise even higher. Therefore, BP control should become a focus of future management efforts in Rwanda.

7.2.5 Mortality of T1D in children and adolescents

We estimated the mortality rate in Rwanda to be between 3.75-18.9/1,000 person years of diabetes, with a 5-year survival rate of 93.8% (10-year survival=82.5%). This is consistent with the results of other mortality studies of T1D in Africa (Ethiopia=15.5/1,000 person years of diabetes,[56] South Africa=84% 10-year survival[155]) but higher than rates from Tanzania (60-71% 5-year survival).[58] Studies from developed countries have reported lower mortality rates than in Rwanda (e.g. 0.06% in the UK),[150–153] though reported rates from Lithuania are within the same range as Rwanda (6.1/1,000 person years of diabetes).[151] 30-year mortality rate of African Americans with T1D is 15.8/1,000 person years of diabetes[87] which is similar to results seen in Rwanda, though with a much longer follow-up period. Unfortunately, background death rates are

unavailable in Rwanda (there is no official death index), so we were unable to calculate SMRs for our population. Though, with the high rate of background death due to communicable disease, malnutrition and violence, the SMR in Rwanda may be relatively low.

While hypoglycemia was the most commonly reported cause of death in Rwandan T1D patients, diabetic ketoacidosis (DKA) was the main cause of death in most studies from developed countries[150–153,179] and Africa.[56,58] A diagnosis of DKA as a cause of death would have been very difficult to make in Rwanda, since most deaths occurred outside of a hospital, and autopsies are rarely done. Additionally, over half of those who died had an unknown cause of death so it is quite possible that hypoglycemia was not actually the main cause of death in Rwanda. Even so, it is clear it is an issue that needs to be addressed in this population. This problem, however, is further exacerbated by the high rate of food insecurity in this population and the low frequency of at home glucose monitoring. These circumstances make it very difficult to achieve optimal glycemic control while avoiding hypoglycemia and possible death.

In our Rwanda cohort we saw a 24-28% increased risk of mortality with each additional year in age at diagnosis. A somewhat smaller (14%) association with age at diagnosis was seen in a study of mortality of T1D in Estonia, Lithuania, and Finland.[151] While the study from the Baltic region did not propose a reason for this conferred risk, we hypothesize that the excess risk associated with advanced age at diagnosis in our cohort was actually due to the effects of surviving for several years with undiagnosed diabetes. Therefore, by the time diabetes was finally diagnosed, the patient was in very bad health and therefore at increased risk of dying. Due to lack of records from time of diagnosis, we cannot confirm this at this time, however our additional findings that higher weight at baseline was protective supports this idea as we have previously documented that those with worse control have lower weight which is likely due to

lack of insulin and dehydration hypovolemia.[118] This finding further emphasizes the importance of improved diagnosis and diabetes awareness in this population.

Though the mortality rates in Rwanda are higher than desired, we have also identified some temporal improvements in survival, as other studies have.[152,154] Those who were first seen for a clinic visit in 2009 had a higher mortality rate than those seen in years since, suggesting that adjustments to management and care made in the years since, have reduced the risk of mortality. Seeing a significant change in such a short time, gives hope to future and further decreases in mortality risk in this population.

7.3 STRENGTHS AND LIMITATIONS

There are several strengths of the current study that should be noted. This is the very first report on the current status of youth and adolescents with T1D in Rwanda. We are the first group to: attempt to estimate the burden of this disease (incidence and prevalence), to estimate the prevalence of complications, and to estimate the mortality due to this disease in Rwanda. To complete this study we used multiple years of clinic data from over 500 participants with T1D, and this appears to be the largest cohort of T1D youth to be studied in sub-Saharan Africa. Even with the earlier reported issues with loss to follow-up, we saw similar loss to follow-up (18.7%) as in Tanzania (11%),[58] and less than rates reported from Ethiopia (33.4%)[56] and South Africa (27.3%).[155] These reports also present a unique contemporary review of the T1D situation in Africa, as most of the previous work was completed over a decade ago.

Several additional weaknesses should also be noted. Unfortunately, our studies were limited to data from cases that were previously clinically diagnosed. We had no screening ability

and were therefore unable to identify any new cases on our own. This left us completely dependent on the local hospital staff for diagnosis. As mentioned before, this limits the generalizability of our rates, and it is very likely that our rates are an underestimation of the true burden of T1D due to the likelihood of death before diagnosis, misdiagnosis, and under-diagnosis, particularly in the earlier years.

Complication status was also not fully or consistently ascertained in this population. A/C ratios were to be collected annually (or more frequently if they had been abnormal), but it appears this was not done consistently, partly due to reagent supply logistics. Additionally, there were logistical issues with limited availability of testing reagents. Therefore, due to irregular testing and lack of follow up for positive results, the rates of complication in this population may be quite different than what we have reported. We were also unable to screen for retinopathy in this population. Previous studies from developed countries and Africa (Ethiopia=9.5%[56], Tanzania=22.2%[57], South Africa=58.8%[65]) have reported the presence of retinopathy in youth cohorts, and therefore it is highly likely that there are children in Rwanda that are affected by this complication. This is especially true with the elevated HbA1c and hypertension present in our population, as they have both previously been identified as risk factors for retinopathy.[66] In Rwanda, we have already noted the presence of several visual complications such as reported cataract surgery and significantly impaired visual acuity. However, recent efforts have been made to make screening available to address this issue further. Additionally, screening for cardiovascular complications was limited. We were not able to collect any lipid data, nor were we able to perform any additional cardiac evaluations. While it is good that we have not had reports of macrovascular events, considering the young age and short duration of diabetes in our cohort, previous studies from developed countries have found that 23% of children and

adolescents with T1D (mean age 14 years, diabetes duration of 6 years) have longer QTc intervals which is a sign of possible cardiac autonomic neuropathy.[180] Thus, suggesting that early signs and symptoms may already be present in our cohort.

It is likely that our data have been affected by a survival bias. Due to the likelihood of missed and undiagnosed cases, as well as loss to follow-up, our results likely represent those of a survivor cohort. Therefore, our results may actually report a better current status than is true. It is likely that the true T1D situation in Rwanda is one of worse control, higher complication rates, and higher mortality.

7.4 FUTURE WORK

Future work with T1D in Rwanda should be focused on continuing the practices that have already been shown to be effective (home monitoring of glucose, use of HbA1c tests, increased education, and frequent clinic visits), and addressing the aforementioned limitations.

The first step should involve the initiation of either a national diabetes registry or official and regular record collection on T1D at the hospital level. We have seen such registries and data collection at hospitals for communicable diseases such as HIV, malaria, and tuberculosis. Therefore, we know the staff has the knowledge and ability to collect such data regularly. However, government involvement and mandates will likely be necessary in order to motivate and direct this effort. This type of system would allow for confirmation of previously reported dates (birth, diagnosis) and future collection of data at the time of diagnosis, not several years post. Providing proper diabetes care as well as follow-up of patients would also be easier to conduct from a local district hospital rather than from the ARD location in Kigali City. This would allow for more thorough follow-up, more consistent care, and better mortality reporting.

This formal diabetes registry and systematic data collection could then be used as the data source for a more formal evaluation of the prevalence and incidence of T1D in Rwanda. With financial support from the government or an official outside funding source, these more complete datasets could then be used to expand upon our 6-district estimation to allow for a countrywide report on T1D rates for all ages and not just children and youth. Additionally, the differences in sex, age at diagnosis, cause of death and level of glycemic control and hypertension could be further examined to see if they persist. These reports would be much more generalizable and the systematic data collection would limit the current effects of survivor bias by promoting earlier and more correct diagnosis.

Additional efforts should be made to ensure that all hospitals and T1D patients have access to glucometers or urine glucose testing supplies. The LFAC program could continue to assist with supplying these meters and the ARD staff can distribute and train the local staff on proper use. This increased availability would need to be supported by availability of testing strips and education on how to properly adjust insulin doses based on testing results. If glucometers are not practical, hospitals should at the very least be supplied with the less expensive urine glucose testing supplies. Additionally, a protocol should be in place at each point of care to test the glucose levels of all sick children.

General diabetes education should also be a major focus of community work to increase awareness of diabetes in the medical society, allowing for more timely and correct diagnoses. Additional education efforts should be focused on the families, schools, and communities around those with T1D so that some of the stigma associated with diabetes may be removed, and more proper management can be obtained.

Laboratory resources need to be improved to allow for better, more regular, and more thorough complication assessment. Official ledgers should be kept that document the status of the stock of DCA reagents, and there needs to be a system in place to order supplies in a more timely fashion to avoid any times where the supplies are not available. Clinic files should be regularly referenced for the date and result of the last complication screening to promote regular screening and confirmation of positive results. Data on lipid profiles, cardiac and additional neuropathy risk factors, and retinopathy need to be collected in the future. C-peptide levels as well as other immune markers need to be quantified to allow for proper classification of diabetes type, so that the best clinical care may be provided. This is especially important in this community given the previous descriptions of atypical diabetes in Africa.

Such a systematic and regulated program would require involvement, support, and oversight from the government, which to this date, they have been hesitant to provide. However, in order for such care to be sustainable long-term, these adjustments will need to be made. As developing countries progress through the epidemiologic transition from focusing on communicable diseases to chronic, they will need to re-assess their current healthcare systems and make the necessary changes to allow for provision of long-term care.

7.5 PUBLIC HEALTH IMPLICATIONS

Each year, an estimated 8-14 million people die of non-communicable diseases in developing countries (Diabetes Atlas, 2009). The WHO predicts that this rate will rise by 17% in the next several years, with the greatest increase in African countries (27%) of low- and middle- income. An estimated 285 million people had diabetes in 2010 and is expected to increase to 483 million by the year 2030.[2] Of these cases, 480,000 were under 14 years of age and had T1D, with 76,000

more diagnosed each year. In Rwanda, we estimate that there are 1,192 (95% CI, 1,061-1,337) children and adolescents under the age of 26 years with T1D, with an annual incidence rate of around 2.2% (95% 1.6-3.0), indicating the total number of cases will rise into the future. Thus, this is a public health issue of growing importance in developing countries as they will have to work to balance the need to provide care for both communicable and chronic diseases. Even with improvements in diabetes care and management, patients with T1D continue to develop complications, and mortality due to T1D is higher than the general population. This disease continues to put a strain on healthcare systems, and will become an even larger problem as the incidence increases with time. In resource poor developing countries, this will likely put an additional strain on an already taxed healthcare system. Therefore, in order to accurately address the growing issue of T1D in Rwanda, we need to better understand the true burden of the disease (incidence/prevalence), how it presents and progresses, and how to prevent early mortality. We have also identified the need for a more sustainable, government supported, program that will result in more complete coverage of the country and will ensure the provision of proper care long-term.

Through our work in Rwanda, we have identified gaps in current care and research, as well as several practices that have proved to be effective. We have also shown that even in a resource poor area, education, HbA1c testing, self-monitoring of glucose and proper insulin adjustments along with regular clinic visits can lead to improved glycemic control. We have identified hypertension and hypoglycemia as complications that need to be addressed in the near future. Our work has also highlighted the need for complete, clean, and regular data collection as well as thorough follow-up practices for improved retention. Unfortunately, due to the current

lack of typology determining resources in Rwanda, we cannot confirm the type of diabetes present in this population, which limits our ability to provide the best care to all patients.

We hope our findings will assist in directing future public health diabetes care efforts in Rwanda as well as other countries as they work towards improving the quality and length of life for children and adolescents with T1D. Though much work still needs to be done to provide the best care to these patients, we believe that our work will provide the groundwork for future efforts.

APPENDIX A: SUPPLEMENTAL TABLES AND FIGURES FOR PAPER 1

Table 18. Baseline characteristics of the 2009-2010 LFAC cohort overall, stratified by attendance at one- and two- year visits and age. Data are stratified by age (over 18 years, under 18 years).

	Overall	Attendance at V1		Attendance at V2	
		Yes	No	Yes	No[&]
<18 years (N)	93	71	22	57	15
Height Z-score	-1.6±1.8	-1.8±1.8	-1.0±1.7 ∓	-1.7±1.8	-1.3±1.7
Short Stature %(n)	48.2 (42)	52.3 (34)	36.4 (8)	46.2 (24)	42.9 (6)
Normal Stature %(n)	47.1 (41)	44.6 (29)	54.6 (12)	51.9 (27)	50.0 (7)
Tall Stature %(n)	4.6 (4)	3.1 (2)	9.1 (2)	1.9 (1)	7.1 (1)
BMI Z-score	-0.7±1.4	-0.7±1.4	-0.7±1.1	-0.6±1.6	-0.6±0.8
Underweight %(n)	16.1 (14)	16.9 (11)	13.6 (3)	15.4 (8)	14.3 (2)
Healthy Weight %(n)	74.7 (65)	72.3 (47)	81.8 (18)	71.2 (37)	85.7 (12)
Overweight %(n)	5.8 (5)	6.2 (4)	4.5 (1)	7.7 (4)	0.0 (0)
Obese %(n)	3.4 (3)	4.6 (3)	0.0 (0)	5.8 (3)	0.0 (0)
Systolic BP Z-score	-0.1±1.0	-0.04±1.1	-0.4±0.7	-0.2±1.0	-0.1±0.8
Normal Systolic BP %(n)	88.5 (77)	86.2 (56)	95.5 (21)	90.4 (47)	92.9 (13)
Pre-Hypertension %(n)	9.2 (8)	10.8 (7)	4.6 (1)	5.8 (3)	7.1 (1)
Hypertension %(n)	2.3 (2)	3.1 (2)	0.0 (0)	3.8 (2)	0.0 (0)
Diastolic BP Z-score	0.5±0.7	0.5±0.7	0.4±0.6	0.5±0.7	0.4±0.6
Normal Diastolic BP %(n)	82.8 (72)	83.1 (54)	81.8 (18)	80.8 (42)	92.9 (13)
Pre-hypertension %(n)	13.8 (12)	12.3 (8)	18.8 (4)	13.5 (7)	7.1 (1)
Hypertension %(n)	3.4 (3)	4.6 (3)	0.0 (0)	5.8 (3)	0.0 (0)
≥ 18 years (N)	192	143	49	87	55
BMI	21.1±4.0	21.0±3.8	21.2±4.6	21.4±3.9	21.2±5.0
Underweight %(n)	21.2 (39)	22.8 (31)	17.0 (8)	20.0 (16)	24.1 (13)
Healthy Weight %(n)	72.3 (133)	70.6 (96)	76.6 (37)	71.2 (58)	68.5 (37)
Overweight %(n)	4.9 (9)	5.2 (7)	4.3 (2)	7.5 (6)	3.7 (2)
Obese %(n)	1.6 (3)	1.5 (2)	2.1 (1)	1.2 (1)	3.7 (2)
Systolic BP (mmHg)	116±16	115±14	120±19	115±16	118±15
Diastolic BP (mmHg)	74±11	74±11	75±12	75±11	76±10
Hypertension %(n)	16.5 (31)	15.7 (22)	18.4 (9)	16.1 (14)	14.5 (8)

[&]Includes only those who were eligible for a two-year follow -up

* Indicates significance at $\alpha < 0.05$

∓ Indicates borderline significance at $\alpha < 0.1$

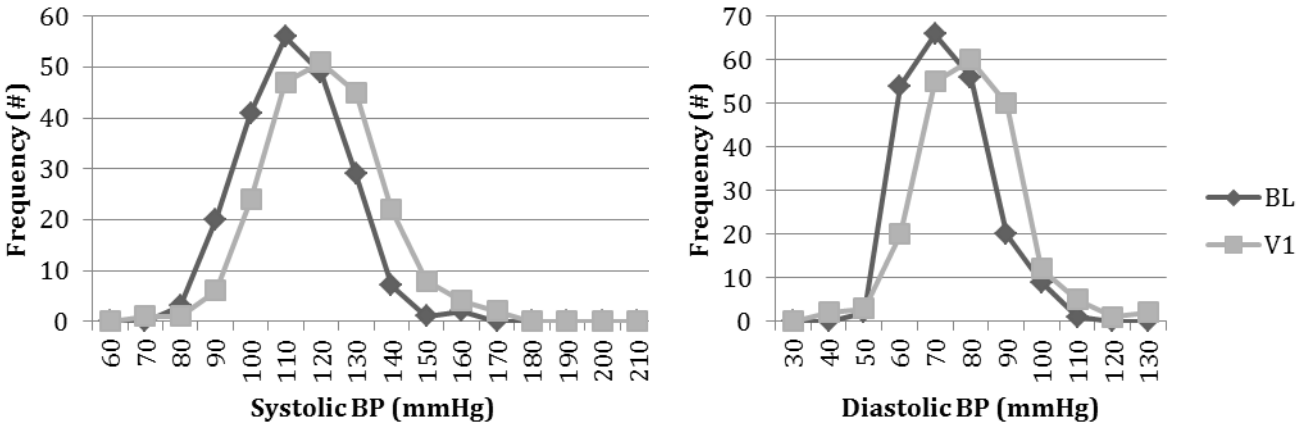
Table 19. Clinical characteristics of one- and two- year follow up visits as compared to baseline and one-year. Data are stratified by age (over 18 years, under 18 years).

	V1		V2		
	Baseline	V1	Baseline	V1	V2
<18 years (N)	62	62	37	29	37
Height Z-score	-1.8±1.9	-1.8±1.9	-1.3±1.6	-1.8±1.8	-1.4±2.0
Short Stature %(n)	55.4 (31)	52.5 (31)	39.4 (13)	40.7 (11)	37.8 (14)
Normal Stature %(n)	41.1 (23)	44.1 (26)	57.6 (19)	55.6 (15)	56.8 (21)
Tall Stature %(n)	3.6 (2)	3.4 (2)	3.0 (1)	3.7 (1)	5.4 (2)
BMI Z-score	-0.7±1.4	-0.6±1.4	-0.4±1.4	-0.4±1.6	-0.4±1.1
Underweight %(n)	16.1 (9)	18.3 (11)	9.1 (3)	10.7 (3)	13.5 (5)
Healthy Weight %(n)	73.2 (41)	70.0 (42)	78.8 (26)	78.6 (22)	78.4 (29)
Overweight %(n)	5.4 (3)	10.0 (6)	6.1 (2)	7.1 (2)	8.1 (3)
Obese %(n)	5.4 (3)	1.7 (1)	6.1 (2)	3.6 (1)	0.0 (0)
Systolic BP Z-score	-0.07±1.0	0.3±1.3*	-0.3±0.9	0.7±1.3*	0.6±1.2$^{\lozenge}$
Normal Systolic BP %(n)	87.5 (49)	79.3 (46)	93.9 (31)	73.1 (19)	75.0 (27)
Pre-Hypertension %(n)	10.7 (6)	5.2 (3)	3.0 (1)	3.8 (1)	11.1 (4)
Hypertension %(n)	1.8 (1)	15.5 (9)*	3.0 (1)	23.1 (6)*	13.9 (5)
Diastolic BP Z-score	0.4±0.7	0.8±1.0*	0.5±0.7	0.8±1.0	1.4±1.0*$^{\lozenge}$
Normal Diastolic BP %(n)	83.9 (47)	67.2 (39)	75.8 (25)	65.4 (17)	47.2 (17)
Pre-hypertension %(n)	12.5 (7)	10.3 (6)	18.2 (6)	7.7 (2)	11.1 (4)
Hypertension %(n)	3.6 (2)	22.4 (13)*	6.1 (2)	26.9 (7)*	41.7 (15)$^{\lozenge}$
≥ 18 years (N)	143	143	87	79	87
BMI	21.0±3.8	21.0±2.6	21.4±3.9	21.4±2.5	21.6±2.8
Underweight %(n)	22.8 (31)	19.6 (27)	20.0 (16)	16.2 (12)	15.3 (13)
Healthy Weight %(n)	70.6 (96)	74.6 (103)	71.2 (57)	75.7 (56)	75.3 (64)
Overweight %(n)	5.2 (7)	5.8 (8)	7.5 (6)	8.1 (6)	9.4 (8)
Obese %(n)	1.5 (2)	0.0 (0)	1.2 (1)	0.0 (0)	0.0 (0)
Systolic BP (mmHg)	115±14	122±15*	115±16	121±14*	122±21$^{\lozenge}$
Diastolic BP (mmHg)	74±11	79±13*	75±11	78±14*	80±14$^{\lozenge}$
Hypertension %(n)	15.7 (22)	56.9 (82)*	16.1 (14)	55.7 (44)*	50.6 (44)$^{\lozenge}$

* Indicates significance at $\alpha = 0.05$ to year before

$^{\lozenge}$ Indicates significance at $\alpha = 0.05$ to two -years before

A. Baseline – V1



B. Baseline – V2

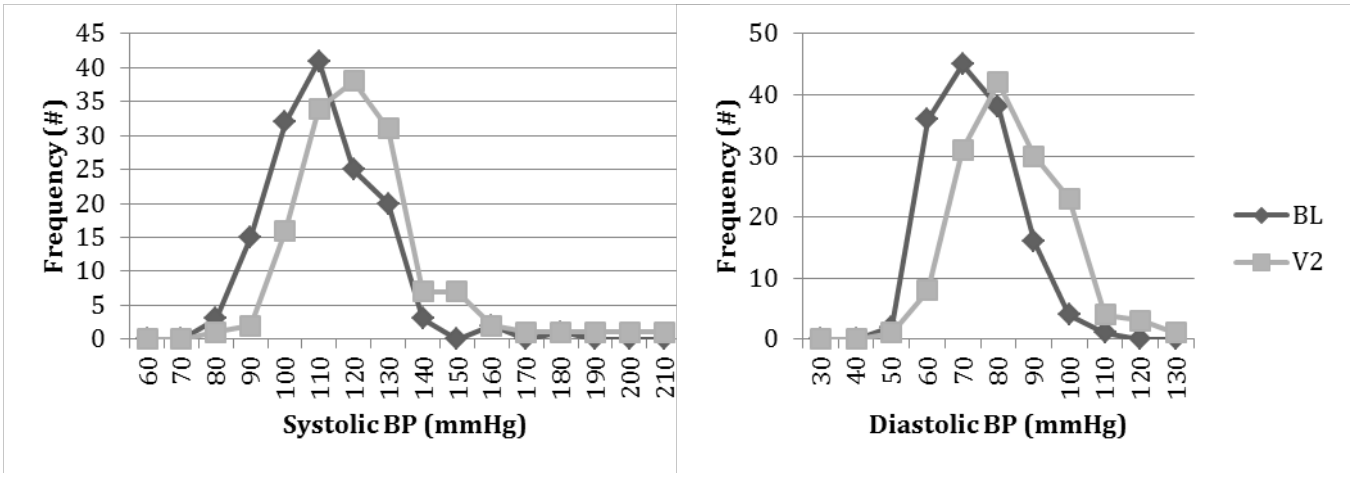


Figure 7. Changes in the distribution of Systolic and Diastolic BP from Baseline to V1 (A) or V2 (B).

APPENDIX B: SUPPLEMENTAL TABLES FOR PAPER 2

Table 20. Age-specific prevalence rates of clinically diagnosed type 1 diabetes in six Districts and Kigali City, Rwanda and mean age at diagnosis.

	Rubavu	Gakenke	Rusizi	Huye	Muhanga	Kigali	**TOTAL**
1-4 Years	0	0	0	0	0	2	**2**
Per 100,000	0.0 (0.0-8.0)	0.0 (0.0-6.4)	0.0 (0.0-6.4)	0.0 (0.0-10.7)	0.0 (0.0-9.5)	1.9 (0.2-7.0)	**0.6 (0.07-2.1)**
Age at Diagnosis	-	-	-	-	-	2.0±1.4	**2.0±1.4**
5-9 Years	1	1	1	0	0	5	**8**
Per 100,000	2.1 (0.04-11.7)	2.4 (0.05-13.3)	1.8 (0.03-10.2)	0.0 (0.0-10.0)	0.0 (0.0-8.5)	4.7 (1.5-11.0)	**2.4 (1.0-4.8)**
Age at Diagnosis	3.0	7.0	5.0	-	-	4.8±2.4	**4.8±2.0**
10-14 Years	2	5	3	1	4	20	**36**
Per 100,000	4.7 (0.6-17.1)	13.0 (4.2-30.5)	6.1 (1.2-18.0)	2.8 (0.06-15.9)	10.4 (2.9-26.6)	23.1 (14.1-35.7)	**12.4 (8.7-17.2)**
Age at Diagnosis	10.0±4.2	9.4±2.6	7.3±7.0	3.0	5.2±5.2	9.4±2.6	**8.6±3.6**
15-19 Years	3	14	9	9	6	24	**71**
Per 100,000	7.6 (1.5-22.3)	34.6 (18.8-58.1)	19.7 (9.0-37-4)	28.6 (13.0-54.3)	17.7 (6.5-38.3)	25.3 (16.3-37.7)	**24.8 (19.4-31.4)**
Age at Diagnosis	14.0±2.6	14.6±2.3	15.4±1.3	14.4±3.1	12.8±6.4	13.4±2.8	**14.0±3.0**
20-24 Years	11	14	17	15	26	63	**158**
Per 100,000	33.3 (16.6-59.6)	43.4 (23.6-72.9)	43.7 (25.4-70.0)	50.1 (28.0-82.5)	76.9 (50.3-112.7)	50.7 (39.0-64.9)	**54.1 (46.0-63.1)**
Age at Diagnosis	16.6±4.2	18.2±2.7	18.0±3.5	17.8±3.9	15.6±3.2	16.7±3.6	**16.9±3.5**
25 Years	0	3	6	2	5	12	**29**
Per 100,000	0.0 (0.0-66.9)	40.4 (8.1-118.7)	84.8 (31.1-183.8)	34.9 (4.2-125.7)	79.3 (25.4-185.5)	43.9 (22.7-76.9)	**48.8 (3.7-70.1)**
Age at Diagnosis	-	19.3±3.8	22.5±1.7	19.0±5.6	20.7±4.9	19.7±4.2	**20.3±3.9**

Table 21. Yearly incidence (per 100,000) estimate of clinically diagnosed type 1 diabetes, by age range at diagnosis, in Rwanda Africa.

Year	1-4 Years	5-9 Years	10-14 Years	15-19 Years	20-24 Years	25 Years
2004	0.36 (0.07-2.0)	1.1 (0.2-3.3)	0.85 (0.1-3.1)	2.6 (1.0-5.6)	0.0 (0.0-1.6)	0.0 (0.0-7.7)
2005	0.35 (0.07-2.0)	1.4 (0.4-3.7)	2.5 (0.9-5.4)	4.6 (2.3-8.3)	0.41 (0.0 -2.3)	0.0 (0.0-7.5)
2006	0.69 (0.08-2.5)	0.0 (0.0-1.3)	2.0 (0.6-4.7)	3.7 (1.7-7.0)	2.0 (0.6-4.7)	0.0 (0.0-7.2)
2007	0.0 (0.0-1.2)	1.4 (0.4-3.5)	3.9 (1.9-7.2)	7.9 (4.8-12.2)	1.9 (0.6-4.5)	0.0 (0.0-7.0)
2008	0.33 (0.07-1.8)	0.33 (0.07-1.9)	1.9 (0.6-4.4)	8.1 (5.0-12.4)	4.5 (2.3-7.9)	0.0 (0.0-6.9)
2009	0.0 (0.0-1.2)	0.97 (0.2-2.8)	0.74 (0.09-2.7)	4.5 (2.3-7.9)	6.2 (3.6-10.0)	1.8 (0.36-10.1)
2010	0.62 (0.07-2.2)	0.94 (0.2-2.8)	2.9 (1.2-5.7)	5.8 (3.3-9.5)	6.8 (4.1-10.6)	0.0 (0.0-6.5)
2011	0.0 (0.0-1.1)	0.61 (0.07-2.2)	3.5 (1.7-6.4)	4.6 (2.4-7.9)	5.2 (2.9-8.6)	1.7 (0.34-9.6)

APPENDIX C: SUPPLEMENTAL TABLE FOR PAPER 3

Table 22. Mortality comparisons for Rwanda and other studies

Country	Crude Mortality (%) (95% CI)	Mortality per 1,000 Person Years (95% CI)	5-Year Survival (%)	10-year survival (%)
Rwanda	6.9 (4.5-10.2)	13.9 (9.0-20.6)	93.8	82.5
Rwanda (Worst case scenario)	32.1 (27.0-37.1)	40.2 (32.0-49.9)	85.1	66.2
Rwanda (Best case scenario)	5.0 (3.3-7.4)	12.3 (7.9-18.1)	-	-
Ethiopia	-	15.5	-	-
South Africa	-	-	-	84
Tanzania	-	-	71-60	-
United Kingdom	0.6	-	-	-
Lithuania	0.04	6.1	97.3	94.0
Estonia	0.02	3.7	99.0	94.3
Finland	0.006	0.8	99.8	99.1
US African Americans (30-years)	-	15.8	98	96

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